Clinical trials in regenerative medicine: negotiating process, practice and outcomes

RUCHI HIGHAM
PhD

University of York
Sociology
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Abstract

There has been significant progress in the basic science of regenerative medicine over the past two decades, but clinical translation has been more halting. Clinical trials are a key step in the translational process and have been highlighted as a particular challenge for the field. This thesis adopts an analytical framework informed by Jasanoff's idiom of co-production to investigate trials of one particular type of regenerative medicine: cell therapies. A mixed-methods design was used, which included quantitative analysis of secondary data, 17 semi-structured interviews with cell therapy trialists, and a longitudinal observational study of a cell therapy trial. The findings indicate that the cell therapy trials landscape in the UK is small, fragmented and dominated by academic-led, publicly-funded studies. This conflicts with a policy environment that is largely aligned with a commercial development model, and a trials process that was designed for drug trials funded by large corporations. Trials tend to be affected by a specific set of local factors, the most important being financial constraints, the logistics of working with cells, the temporality of the trial and the need to align the work of disparate domains. These issues create a challenging translational environment, with the linearity and abstracted nature of the trials process conflicting with the recursive, situated nature of innovation. They also highlight the significant contingency involved in trials, which is at odds with the priority evidence-based medicine places on this supposedly neutral, objective method. Whilst cell therapy trials must without a doubt be held to the highest regulatory standards, it is also important that the clinical research framework takes into account the challenges they pose and the contingent nature of the evidence they generate, and the thesis concludes with some recommendations as to how this might be achieved.

Contents

List of tables

List of figures

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Author's declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, university. All sources are acknowledged as references.

Based on some of the work within this thesis, the following paper has been published:

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1. Introduction

Regenerative medicine, like tissue engineering before it, is a field characterised by high expectations that remain (as yet) largely unfulfilled. The past two decades have seen significant progress in basic scientific research, such as the full mapping of the human genome, the isolation of human embryonic stem cells, and the discovery of the CRISPR process for gene editing. So far, however, effective treatments in widespread clinical use have failed to materialise. The recent history of clinical regenerative medicine is largely one of setbacks rather than breakthroughs - for instance, the move away from neural cell transplantation for Parkinson's Disease after early trials failed to demonstrate efficacy, and the early closure of the first clinical trial to use human embryonic stem cells (hESCs) after the company sponsoring the trial, Geron, discontinued its stem cell research programme. The halting progress of clinical regenerative medicine is exemplified by the fact that only eight advanced therapy medicinal products (ATMPs) had received marketing authorisation from the European Medicines Agency (EMA) at the time of writing (June 2017). Of these, four have since been suspended or withdrawn, leaving only four ATMPs currently authorised for use in Europe. Thus, although regenerative medicine is generally thought to have great potential for both public health and wealth creation, there is a growing recognition that there are significant obstacles to be overcome if this potential is to be realised. In 2013, a House of Lords Science and Technology Committee report on regenerative medicine concluded that: "regenerative medicine has the potential to save lives and to help support the UK economy … but the UK is currently underprepared to realise the full potential of regenerative medicine. The many words which have been spoken about regenerative medicine must translate to action, and quickly." Five years later, however, a House of Commons Select Committee report concluded that although progress has been made towards a comprehensive strategy for delivering regenerative medicine, there is still "much work to be done" (House of Commons, 2017).

The 2013 House of Lords report highlighted a number of challenges which have impeded innovation in regenerative medicine, one of which was the design and

conduct of clinical trials. The Regenerative Medicine Expert Group (RMEG) set up to address the House of Lords' recommendations found little progress had been made (RMEG, 2015). More recently, the 2017 House of Commons report reiterated both the difficulties of trialling and the lack of progress in this area. The House of Commons report also highlighted the opportunity to change UK regulations following departure from the EU, particularly in the area of Hospital Exemption, which offers another potential route for 'trialling' regenerative medicines in the clinic.

Clinical trials are in some ways a bridge between the lab and the clinic, and thus are a key element of so-called translational medicine (Webster, 2013, p.81). As such, the in-depth study of clinical trials that I present in this thesis not only provides insight that could help to overcome the translational challenges faced by the field of regenerative medicine, it also provides a lens through which to examine the dynamics of innovation and translation more broadly. I examine how clinical trials fit into the innovation process for one particular type of regenerative medicine (cell therapies), looking at how, why and to what extent trials are challenging for translation, and how these challenges might be overcome. In this introductory chapter I will introduce my theoretical and analytical framework, provide a brief background to translational cell therapy research, and detail the specific research questions and how they are addressed in the remainder of the thesis. Before this, however, I will explain the institutional context of my research, which was undertaken as part of a multidiscipline studentship pilot programme.

1.1 Institutional context: (multi) disciplinary expectations

The Economic and Social Research Council (ESRC) award that funded this PhD was one of three multidisciplinary studentships offered as part of a pilot programme. The information provided to applicants explained that the aims of these studentships were "creating a community of social scientists capable of making valuable contributions to wide-ranging debates in the UK and beyond, and the production of innovative social science knowledge impacting in the arena of science and society" (ESRC, 2013). The multidisciplinary elements of the awards included joint supervision (in my case in sociology and biology), substantive training in biology and health

sciences as well as sociology, and participation in the Biotechnology and Biological Sciences Research Council (BBSRC) Doctoral Training Partnership as well as the ESRC White Rose Doctoral Training Centre. Throughout the four-year studentship I undertook a range of activities intended to facilitate and support the multidisciplinary nature of the research, including auditing an MSc module in biology, taking part in the regular meetings held by my biology supervisor's lab team, completing a Medical Research Council training course on cell therapy trials and attending various conferences and workshops aimed at students and researchers undertaking scientific and clinical cell therapy work. Thus although I was primarily based in sociology, from the beginning I was exposed to and engaged with a variety of different disciplinary perspectives.

I found my engagement with the different disciplines extremely interesting, and it gave me a very thorough understanding of both the scientific aspects of cell therapies and sociological approaches to the topic. However, I quickly began to experience what Lyle (2016) calls "the epistemological and theoretical void" between the social and natural sciences. To give an example, during the first few weeks I attended a poster presentation which reported the work of doctoral students in the biology department, with a view to finding areas of relevance to my own research. A number of posters reported the results of research on stem cells, all of which reported the results of laboratory research and made very specific claims about the exact characteristics of the cells, such as whether they expressed a particular marker, without addressing any potential complexity or contingency involved in these claims. In contrast, the sociological literature that I was reading at that time, which also dealt with stem cells, focussed entirely on the discourses and narratives constructed around the term and how these were mobilised by different actors, without engaging at all with the materiality of the cells themselves. Despite both being relevant to my study, and both dealing with similar topic areas, there were no obvious areas of overlap between the two disciplines.

The scale of these ontological, epistemological and methodological differences between sociology and biology made it difficult to conceptualise a study that could reconcile these divergent, and sometimes conflicting, disciplinary

expectations. Furthermore, although my studentship was nominally multidisciplinary there were two important factors that appeared to favour a more mono-disciplinary approach. Firstly, the PhD was funded by the ESRC and would be examined in sociology, clearly giving primacy to the sociological rather than the biological aspects of the research. Secondly, and in line with this, my training as a researcher is in the social sciences so the research design would inevitably be more sociological than bio-scientific. Thus, although my involvement in each individual discipline was informative, and the intention of the studentship was clearly to undertake research that incorporated aspects of both, it was not immediately apparent to me exactly how this should be approached.

Given the pilot nature of the multidiscipline studentship programme there was no precedent to be followed, so I needed to develop my own approach. My first step was to investigate how multidisciplinary research is generally understood and defined in the literature, with a view to finding a working definition that would help to frame my own project. I quickly discovered, however, that there are in fact a multitude of terms used to describe research that crosses disciplinary boundaries, and that the definitions of these terms are both ambiguous and contested (Graff, 2016). The ESRC studentship was specifically described as 'multidiscipline', but this term appears to be most commonly used to describe collaborative work where scholars from different disciplines come together to work on a common problem or research question, with the work that each does remaining within their own disciplinary boundaries (Lyall et al., 2011). Clearly this was not a viable approach for my own work, as doctoral research is by definition conducted by a single researcher. In contrast, Lyall and colleagues define 'interdisciplinary' as "research which approaches an issue from a range of disciplinary perspectives", and Nissani (1997) suggests that it describes work that "combines components of two or more disciplines in the search or creation of new knowledge." This suggests an approach that combines some, but not all, aspects of different disciplines, which would be more achievable by a single researcher. Importantly, Lyall and colleagues also suggest that interdisciplinarity can be viewed as a continuum, and can be relatively stronger or weaker depending on the amount of integration between the disciplines.

Both the mono-disciplinary institutional setting and my own research training background suggested that a relatively weak interdisciplinary approach would be most suitable for my study. This then is how I position my research - as a sociological study that addresses a sociological audience, but that draws on and engages with perspectives from biology and health sciences, intending to be both understandable and relevant to these disciplines as well.

After defining the broad framework for the interdisciplinary aspects of my study, I needed to make a number of specific decisions about how to incorporate and do justice to the expectations of the different disciplines. Interdisciplinarity is often associated with applied rather than basic or theoretical research, in part because the pursuit of solutions to problems in the real world both requires, and provides a strong motivation for, collaboration between disciplines (Pohl and Hadorn, 2008). Indeed, Lyle (2016) argues that focussing on a common societal goal which both disciplines can work towards might be the only productive way to approach interdisciplinary research that spans the natural and social sciences. Lyall and colleagues (2011) suggest that there are two different types of interdisciplinary research: academically-oriented and problem-focussed. Academically-oriented research aims to resolve academically-informed questions, tends to emerge when the methodological limits of individual disciplines have been reached, and is highlighted as being particularly difficult for research that spans the natural and social sciences. Problem-focussed research, in contrast, addresses specific issues of relevance to society, has less focus on discipline-related outcomes, and can be usefully adopted when there is a gap in analysis or understanding of a practical problem that can be bridged by bringing together insights from more than one discipline. Interdisciplinary studies can focus entirely on one or other approach or can combine elements of both, although normally there would be a greater emphasis on one or the other. Although I incorporate both approaches to some extent there is an emphasis on problem-focussed research, which appeared to be best suited to my study as it is more practical for research that aims to address both the natural and social sciences. A largely problem-focussed approach also aligns most closely with the initial expectations for my studentship, which was positioned in the original ESRC

background information as being specifically intended to address the translational challenges of regenerative medicine (ESRC 2013).

Focussing on a societal outcome is clearly a useful - and possibly essential - approach for successful interdisciplinary research, but it also by implication introduces a normative slant in that it aligns the research with a policy aim, thereby making certain implicit value judgements about what such an aim 'should' be. A normative approach is commonly seen in many disciplines, including social sciences such as economics, social policy and health sciences, but is less common in sociology, and in particular Science and Technology Studies (STS), which has generally adopted a more symmetrical, value-free stance (Fuller and Collier, 2003; Sismondo, 2009). I encountered numerous examples of these differences during my studies; for instance, most of the health sciences and biology and literature I read makes a case for a specific approach to stem cell research, cell therapy policy or clinical trials methods. In contrast, the STS literature tends instead to highlight the contextualised and socially-contingent nature of trials or innovation, with less focus on explicit judgements or recommendations. I also experienced these differences first hand when I discussed or presented my research in different disciplinary contexts. Biologists, clinicians, cell manufacturers and trials professionals were invariably interested in what recommendations I could make, and how things could be 'done better', whereas sociologists tended to ask more conceptual questions, and to actively challenge anything I presented that they viewed as normative. Deciding how to address these divergent expectations was thus one of the most important factors when deciding how to approach the interdisciplinary aspects of my work, and here I found Webster's (2007) conceptualisation of a 'serviceable' STS particularly helpful. Webster highlights the potential role of STS as an intermediary "working at the boundaries of science and society", and argues that STS can move beyond deconstructivism and undertake "reconstructivist engagement with science and science policy making." With this in mind, I adopt an approach whereby I not only examine cell therapy trials from a variety of perspectives, uncovering the multiple agendas and concerns involved, I also then consider the implications of these

different perspectives and use this analysis to make recommendations for the future conduct of trials.

Developing a 'reconstructivist' framework between STS and the natural sciences involved attempting to find areas of mutual interest between them. Contingency, complexity and reflexivity are by no means completely absent from the scientific and health science literature, and differences between the disciplines sometimes appear to be more a matter of emphasis than content. For instance, the scientific community might acknowledge the provisionality of terms such as 'MSC' or 'stem cell', but it will continue to use them as working definitions that allow the scientific debate to move forwards, whereas an STS account might focus entirely on unpicking the terms themselves. Likewise, STS research might examine the social context of trials in order to highlight the contingent nature of clinical research, whereas the health sciences literature might make similar points but with a view to recommending specific improvements to trial design. When it comes to actually integrating the two approaches, however, I often found myself struggling to reconcile the very different ontological positions of the different disciplines. Biology and health sciences tend to lean towards a realist perspective, which assumes a world in which there is one 'truth' that can be accessed through research, whereas sociological research tends to assume a more relativist standpoint, which holds that rather than being universal, 'truth' or 'reality' is in fact dependent on our knowledge and understanding, which emerges from social contexts and processes (Clarke and Braun, 2013).

To locate my study within the broad sociological paradigm it clearly needed to adopt a largely relativist ontological position, but in order to engage with other disciplines, and thus contribute to a genuinely serviceable STS, it was also necessary to accommodate a realist perspective as well. In this endeavour I found the literature on critical realism particularly helpful. Critical realism aims to avoid the extremes of both social and natural determinism, focussing on the relationship between knowledge and reality without affording primacy to either (Fletcher 2016). Two important aspects of critical realism particularly informed my thinking when undertaking this study. The first is the distinction between the 'transitive' and the

'intransitive' dimensions of knowledge: i.e. the objects of our study, which do not change, and the way that we understand these objects, which does (Sayer, 2000). In this way, critical realism allows for objects of study to have objective properties that exist whether or not we observe them, whilst still accounting for the socially-constructed nature of our observations. Fundamental to this, and the second aspect of critical realism that particularly informed my thinking, is an understanding that the actual is determined by emergence - that what comes to be is the product of the intersection of multiple factors, and the specific articulation between these factors determines the characteristics of the actual phenomena produced. In this context, there is value not only in examining the range of empirical representations on a given topic, and the social dynamics of these representations, but also in considering their relative fallibility. Thus a discussion of MSCs, such as the one that I present in Chapter 6, can acknowledge that the scientific knowledge presented is only an empirical representation of reality, whilst also recognising that these cells have real properties that confer a range of potential powers, and that the likelihood and nature of any actualisation of these powers will be determined by interactions with other factors, both social and material. I do not, therefore, uncritically accept a purely realist account of these cells - that what is observed and reported is an infallible representation of what these cells are or can do - but likewise, I am do not limit myself to an entirely symmetrical analysis of the various socially-constructed representations of MSCs, without any consideration of how well they might reflect 'reality'.

As well as having different ontological positions, another significant difference between the disciplines I worked in is their approach to communicating research. In line with a more realist ontological perspective, the natural sciences tend to write in a style that aims to convey clarity, precision and objectivity, whereas sociological research tends to be presented in a much more narrative, discursive style, focused on uncovering subjectivity, complexity and multiple perspectives. Onwuegbuzie and Johnson (2006) suggest two broad approaches for addressing this issue in interdisciplinary research: either changing between the two styles (dualist) or adopting a moderate position that incorporates elements of both (continuum).

Both options have their advantages, but I felt the second was most appropriate for this work for two main reasons. Firstly, unlike larger interdisciplinary projects that have multiple outputs, it would not be possible to adopt two entirely different reporting styles in a PhD thesis without losing some of the internal consistency. Secondly, although this research has interdisciplinary elements it is located within sociology and adopts sociological methods and analytical techniques, therefore there was no need to adopt a scientific writing style that might be needed to discuss methods from other disciplines, such as laboratory research or meta-analysis. I agree with Davis and Abraham's (2013) contention that the job of the social scientist should be to make sense of complexity, and with Howes' (2017) position that clarity is of paramount importance and should be prioritised above the specific conventions of any particular paradigm. With this in mind, I have followed Davis and Abraham's approach of writing for an informed and educated lay person rather than an expert in any particular discipline. This means aiming above all for clarity, avoiding the use of technical terminology or jargon from specific disciplines as much as possible, and where technical terms are used, providing sufficient explanation for the unfamiliar reader.

Another disciplinary challenge that I addressed using Onwuegbuzie and Johnson's continuum approach relates to structure of the thesis, which, as Howes (2017) highlights, is another key difference between the social and natural sciences. Sociological theses tend to unfold somewhat like a monograph, with thematic arcs that are developed throughout a series of chapters, whereas in biology and health sciences the thesis chapters might be more likely to resemble a series of interconnected journal articles, each dealing with a specific question and perhaps even a different set of data or methods.[1] I take a moderate approach here as well, largely following sociological conventions but incorporating some elements of

[1] The different disciplinary expectations of thesis-writing often became apparent during my supervision meetings. For instance, the sociology department requires a significant amount of work to be written up in the first 18 months of a doctoral studentship, which surprised my biology supervisor as the entirety of a biology thesis would typically be written up at the end of the research, just before submission. As he pointed out, writing a scientific literature review two years before submitting the thesis means much of the literature will become out of date, and indeed I have had to revisit many of the scientific (and policy) literature sections at the end of my project.

scientific thesis-writing by focussing each chapter on a specific aspect of cell therapy trials. This allows me to tailor my approach for each chapter slightly to align with the issue being addressed, so for instance chapters 3 and 6, which attend to the industry and scientific issues, adopt a slightly more realist perspective than some of the other chapters.

This approach to the chapter structure also helped me to overcome one of the most pressing practical challenges of interdisciplinary research, which is that in the absence of disciplinary boundaries it can be very difficult to define and limit the scope of the work, and in particular which literature to include (Lyall et al., 2011). This was a challenge from the very beginning of my research; as I engaged with researchers in both sociology and biology I encountered a vast array of literature that dealt with cell therapy trials, and when reading the most prominent STS literature about regenerative medicine I found very few references to scientific or health sciences articles, but I would often later come across papers in a scientific journal that appeared to deal with the same, or very similar issues. Further complexity was introduced by the large body of so-called 'grey literature', including policy documentation, commercial publications and third sector research, much of which dealt with the same issues as the academic literature but in different ways. If adopting an interdisciplinary approach, then, I would clearly not be able to simply review *the literature* on cell therapy trials, I would actually need to find a way of addressing *multiple literatures* that operate in the same space whilst remaining almost entirely independently of each other.

Fuller (2016) specifically addresses the issue of multiple literatures, describing it as a problem of 'undiscovered public knowledge". Using the analogy of an internet search he draws a distinction between data mining, which reinforces preconceived distinctions by "delivering to the user what they are already looking for", and data surfacing, which "aims to 'emancipate' hidden data … independent of any strategic goals or other preconceptions that users might have had for undertaking a search." Data surfacing is a useful concept for interdisciplinary research because it assumes a 'bottom-up' approach to identifying relevant literature, which avoids the preconceptions of approaching a literature search from a particular disciplinary

perspective. This approach aligned with my ontological position, allowing me to incorporate both relativist and realist viewpoints, and also with my aim of contributing to a serviceable STS because it engaged with the range of perspectives within the field itself, rather than being limited to one paradigmatic framework. I therefore decided not to confine my literature search to one particular discipline, or indeed to academic literature *per se*, but rather I read as widely as possible and allowed the emerging themes from my fieldwork to determine which literature I deemed most relevant. Inevitably, this resulted in a much greater volume of literature than a mono-disciplinary approach would have done, making it impractical to present a traditional literature review at the beginning of the thesis. Instead, each chapter reviews and discusses the literature that is most relevant to the theme of the chapter; for instance, Chapter 6, which explores scientific and clinical uncertainty, largely engages with the scientific and health sciences literature, whereas Chapter 4, which examines the social dynamics of trials, foregrounds the way this issue has been addressed by sociological research.

In summary, then, my research is predominantly located within sociology but also incorporates an interdisciplinary element, which affected the study in a number of ways. Firstly, the research is problem-focussed and aims to contribute to a serviceable STS, and as such I present both a sociologically-informed analysis of cell therapy trials and a series of recommendations based on this analysis. Secondly, I adopt an ontological position informed by critical realism, rejecting neither the realist nor the relativist understanding of reality but rather aiming to explore the relationship between the two. This informed both the theoretical perspectives that I draw on, which I will discuss shortly, and the methodological approach that I will set out in Chapter 2. Thirdly, I adopt a continuum approach to the writing and presentation of the thesis, adopting a writing style that is aimed at an intelligent lay reader rather than a disciplinary specialist, taking a slightly more or less realist approach in different chapters depending on the specific themes being addressed (whilst maintaining a broadly reflexive analytical approach throughout), and addressing specifically-relevant literatures in the chapters they relate to rather than presenting a traditional review of 'the literature' at the beginning of the thesis. It is

still necessary, however, to provide the background information and theoretical context that would normally be provided in a traditional literature review, so in the remainder of this introductory chapter I will discuss the theoretical grounding of my research and then provide a brief background to cell therapy trials, before going on to discuss how these informed the research questions addressed in the thesis.

1.2 Theoretical / conceptual framework

The theoretical grounding for my research draws on critiques of randomised controlled trials (RCTs) and evidence-based medicine (EBM), emanating largely from sociology but also from history and philosophy of science and also the health sciences literature. EBM can broadly be described as "the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions" (Rosenberg and Donald, 1995). The concept emerged in the early 1990s in response to perceived variability in clinical care, concerns about the influence of pharmaceutical companies over clinical decision making, and a growing realisation that many commonly-used treatments were not effective and in some cases even harmful (Marks, 1997). Presented as a "new paradigm for medical practice" (EBM Working Group, 1992), early EBM 'manifestos' promoted the use of clinical evidence to determine the efficacy of treatments and argued for reducing the reliance on clinical expertise and background theory. The EBM movement achieved remarkable success from the beginning, with interest in the concept growing "exponentially" in the decade after it was first proposed (Straus and McAlister, 2000). It is now widely accepted as the best way to make medical decisions (Borgerson, 2005), and its model of evidence-based decision making has started to be applied in many other areas, such as social policy, education and economic development (Borgerson and Bluhm, 2005; Cartwright, 2011).

RCTs are presented by proponents of EBM as a neutral method that can be applied in any context to produce objective, value-free evidence. Central to this narrative is the assertion that RCTs are separate from, and immune to, social processes - that they fall within the realm of 'science' rather than 'politics' and are therefore concerned with the pursuit of truth rather than the wielding of power

(Marks, 1997). Sociological critiques have challenged this, however, highlighting the fact that trials are in fact complex, mutable social processes. Setting up and running a trial involves negotiation between numerous actors with differing motivations and values, requires the coordination of many different work processes, and involves various institutional structures, cultures and power relations (Marks, 1997; Mueller, 1997; Will and Moreira, 2010). These practice-based critiques, which I examine in Chapter 4, have explored the complex interactions between patients and clinicians during trials, patients' understanding of their involvement in trials, and the various ways in which commercial concerns shape the conduct of trials. Taken together, they highlight the socially-contingent nature of the trials process, and the extent to which the day-to-day practice of trials is shaped by social interactions, institutional contexts and power dynamics.

These practice-based critiques of RCTs point towards the importance of examining the various ways that trials, and the evidence they generate, are shaped by practice. It is also important, however, to recognise the ways in which trials can shape practice (Will and Moreira, 2010), an issue that is explored in detail by Keating and Cambrosio's work on cancer clinical trials, which documents the development of a new 'style of practice', which they summarise as "a distinctive configuration of institutions, scientific practices, and materials that generates new entities as well as specific ways of identifying and investigating research questions, of producing and assessing results, and of regulating these activities" (Keating and Cambrosio, 2012, p.20). This style of practice draws on, but is distinct from, its constituent domains - such as laboratory or statistical research - and has influenced both clinical practice and research and innovation in cancer treatment. Their research identifies a number of important actors in cancer clinical research, and explores how the developing style of practice affected, and was affected by, each of these groups. For instance, they show how the role of medical oncologist was effectively defined by the developing clinical research process, how statisticians moved from being outside observers to "full-fledged coinvestigators", how patients became "the subject of a network of evolving rules, norms, restrictions, and ethical and epistemological dilemmas", and how characterisations of the disease evolved through the conduct of research

(Keating and Cambrosio, 2007). This conceptualisation of clinical research highlights the fact that individual clinical trials are not distinct entities but are embedded within systems of research and innovation, which have themselves evolved over time.

In addition to the practice-based critiques discussed above, there are also various more 'epistemic' critiques of the EBM framework. One of the most important aspects of EBM is the importance it places on experimental rather than observational evidence, and in particular on evidence generated from RCTs (Dehue, 2010). Various writers have raised concerns about EBM's phenomenal success in exclusively defining and delineating what counts as evidence in healthcare, effectively "colonising" the meaning of the word (Daly, 2005). The concept of evidence is an extremely powerful one; as Edwards (2007) puts it: "Who can argue with evidence? How potent is the orator who claims evidence on his side!" Will and Moreira (2010) raise the concern that given the rhetorical power it controls, EBM leads to a form of "epistemic exclusion", whereby certain populations and problems become 'locked out' of healthcare innovation. EBM's stranglehold on the meaning of evidence thus not only affects the way that specific treatments are perceived, it also has significant implications for innovation in healthcare more broadly, and for the way that health and illness are conceptualised overall. As Borgerson and Bluhm (2005) point out, "standards of evidence, wherever they are designed and employed, serve to shape the direction of the field or discipline in which they are adopted." In particular, a number of writers have highlighted how the EBM framework has led to research money being channelled into areas that lend themselves to RCTs, whilst also shaping medical research around the requirements of the method, for instance limiting the follow up time period and focussing on measurable outcomes (Smith, 1996; Borgerson and Bluhm, 2005; Brody et al., 2005; Edwards, 2007). This is not just a problem with RCTs, but with the fact that all the forms of evidence prioritised by EBM are quantitative, meaning that "health becomes merely the state in which specific quantifiable symptoms or diseases are not present" (Borgerson and Bluhm, 2005). Thus, the specific conceptualisation of evidence promoted by EBM has a structuring effect on healthcare research in general, and on the very definition of what it means to be healthy.

Both the practice-based and epistemic critiques of EBM align with a broader body of work in the field of STS, which over the last five decades has highlighted the extent to which scientific knowledge and technological innovation, rather than being technologically-determined, are shaped by social processes and interactions. In 1962 Kuhn's The Structure of Scientific Revolutions was published, challenging the dominant understandings of science as rational and naturally-determined and turning attention instead to the concept that science actually emerges from 'what scientists do' (Kuhn, 1962). In the 1970s the 'strong programme' of the sociology of scientific knowledge (SSK) began to examine the development of scientific knowledge from a position of methodological symmetry, arguing that scientific beliefs require explanation regardless of whether they are deemed to be rational or irrational, 'right' or 'wrong'. This shifts the emphasis away from 'rational' or 'material' explanations of science and technology and focusses instead on the work undertaken by scientists and the interactions between different actors, underpinning many different strands of work within STS which can broadly be termed 'constructivist' (Sismondo, 2009, p.61). Some of these traditions emphasise how social factors shape scientific knowledge, such as Knorr-Cetina's work exploring how scientists and laboratory practices actively seek to control and structure the natural world, effectively constructing 'facts' that are far removed from the materiality they claim to represent (see for instance Knorr-Cetina 1977, 1999). Other traditions attribute a greater role to material objects, for instance actor network theory (ANT) understands techno-science as emerging from the interests and actions of networks of both human and non-human 'actors' (Sismondo, 2009, p.81). ANT is also an example of the way that STS has challenged linear understandings of technological innovation, which assumes a progression from basic scientific research to technology development and adoption (Godin 2006). STS accounts, however, have highlighted the recursive nature of innovation, and the extent to which factors other than scientific knowledge are important in the development of technological artefacts (Sismondo, 2009, p.93).

Insights from these various traditions and perspectives within STS informed my thinking throughout my research, and in particular when making decisions about

methodology (which I discuss in Chapter 2). From a theoretical and analytical perspective, however, I particularly draw on Sheila Jasanoff's work on co-production. Presented as an 'idiom' which underpins a wide range of work in STS, including ANT and SSK, rather than a formal theoretical framework, co-production argues that scientific knowledge cannot be separated from the context in which it is generated, and focuses attention on the role that that social institutions play in ordering and reordering our understanding of nature (Jasanoff 2004). Jasanoff distinguishes between *constitutive* co-production, which focuses on the construction of science and technology and can be seen in STS theories such as ANT, and *interactional* co-production, which looks more closely at the tensions that emerge as new technologies and knowledge challenge existing practices and regulatory frameworks. Interactional co-production thus examines the epistemic and socio-political aspects of techno-science, showing how these do not develop separately from or as a result of science and scientific progress, but rather both emerge concurrently in one integrated process.

Although both versions of co-production are relevant and useful to an examination of cell therapy trials, I particularly draw on the concept of interactional co-production in my analysis. This concept is reflected in Keating and Cambrosio's style of practice and also in much of the STS literature on regenerative medicine, such as Faulkner's concept of governation (Faulkner, 2009), which he uses to describe the impact of differential and changing regulatory definitions on the development and deployment of Autologous Chondrocyte Implantation (ACI). Jasanoff also describes four common pathways, or 'ordering instruments', of co-production: making identities, making institutions, making discourses and making representations, which are visible in much of the STS literature on regenerative medicine. The concurrent emergence of science and the *institutions* that shape it has been highlighted in research on the UK Stem Cell Bank (Stephens et. al., 2011, 2008a, 2008b) and the Cell and Gene Therapy Catapult (Gardner and Webster, 2017); different *identities*, and the tensions between them, are explored in studies of the 'translational medicine' agenda (for instance Wainwright et al., 2006 and Brosnan and Michael, 2014); the making of scientific *representations*, the ways that these representations travel and

the work that they do are explored in studies of the development of standards, norms and shared understandings of cell therapies (Webster et al., 2011, Eriksson and Webster, 2008, Eriksson and Webster, 2015); and *discourses* are the focus of research highlighting how expectations and 'promissory narratives' about the future potential of cell therapies are deployed to create certain realities in the present (Martin et al., 2008, Kitzinger and Williams, 2005, Brown and Michael 2003).

Another important aspect of Jasanoff's work is her argument that, rather than existing independently of each other, the regulation of science and science itself are inextricably intertwined (see for instance Jasanoff 1990). In the context of uncertain emerging technologies regulatory decision-making is not a rational, objective process, but rather emerges from the attempts of regulators to construct order out of messiness and uncertainty, in which endeavour they rely on the expertise of scientists themselves. STS research has highlighted that just as scientific certainty cannot be entirely explained as rational and materially-determined, so too must uncertainty also be understood in terms of social construction. There is thus no 'real' or 'objective' measure of uncertainty, but rather it must be understood as a conceptual tool that is mobilised in negotiations about the credibility, validity and usefulness of scientific knowledge. Thus, uncertainties create an area of "interpretive subjectivity" in which various actors can promote agendas that conform to their interests (Jasanoff and Wynne 1998).

Wynne (1992) provides a useful classification of risks and uncertainty, distinguishing between *risk*, which can be measured and predicted, *uncertainty*, which relates to gaps in knowledge that are known and have understood parameters, *ignorance*, which arises from gaps in knowledge that are not known or have undefined parameters, and *indeterminacy*, which relates to the causal chains or outcomes of decisions being open. Wynne makes two important arguments about this conceptualisation of uncertainty: firstly, that ignorance is endemic in, and fundamental to, scientific research, and only becomes problematic when scientific knowledge is "institutionalised in policy making" without recognition. Secondly, he argues that rather than uncertainty, ignorance and indeterminacy representing a

continuum they are in fact overlaid over one another, and are expressed relative to the "decision-stakes", which are themselves conditional, and thus indeterminate.

Wynne focuses on how uncertainties are defined, represented and mobilised at a conceptual level, which provides a useful framing for other research in STS which has explored the ways that emerging technologies create new and unpredictable uncertainties in practice. For instance, Mesman (2008) explores how neonatal diagnostic and prognostic innovations have led to new treatment options but have also raised new questions about the treatment and prospects of ill babies, and about which voices and evidence should be given most weight in decision making. In another example, Franklin and Roberts (2006) examine the rise of preimplantation genetic diagnosis, which they show to be a complex and multi-layered phenomenon which is a technological solution to reducing and 'controlling' uncertainty, but in another sense an uncontrolled and uncertain process that introduces new and contested moral choices, meanings, possibilities and clinical possibilities. How various stakeholders respond to and mobilise the new uncertainties thrown up by emerging technologies thus has profound implications both for day-to-day clinical practice and for the regulatory and policy frameworks that shape it.

Unlike some branches of STS, which focus primarily on the emergence of science and technology from the day-to-day practice of science, the idiom of co-production encourages an examination of the political and societal aspects of knowledge governance, and the implications of these for both techno-science and society. It does not take an entirely constructivist or socially-deterministic position, focussing instead on the way that science and society are mutually-configuring. As such it aligns with the epistemic critiques of EBM discussed above, and also with my broad ontological position. This conceptual framework informs many aspects of the thesis, in particular my analytical approach (which I discuss in Chapter 2), the discussion of the policy and regulatory framework in Chapters 3 and 4 and the consideration of different versions of evidence in Chapter 7. The related concepts of uncertainty, ignorance and indeterminacy likewise influenced much of the analysis, but are particularly deployed in Chapter 5, which explores the uncertainties inherent in working with cells, and in Chapter 6, which examines the way that trialists and

scientists conceptualise and reconcile uncertainty in trials, and how this interacts with the translational process. The practice-based critiques of trials, along with the broader STS framework discussed above, direct the analyst's attention to the 'doing' of trials, an approach which underpins the whole thesis and particularly informs the methodological approach (discussed in Chapter 2) and the analysis of challenges presented in Chapter 5. These critiques, and in particular the style of practice concept, provide a useful model for exploring the various ways in which clinical research shapes and is shaped by social context, and the resulting effects on medical practice and innovation. I draw on this framework in Chapters 3 and 4 to analyse the characteristics and social dynamics of cell therapy trials and I then return to the style of practice concept in the concluding chapter, where I consider my analysis in the context of Keating and Cambrosio's findings. I also return to the concepts of co-production and uncertainty in the concluding chapter, where I draw together the key themes from throughout the thesis and consider their implications both in the context of the STS literature and for the future of cell therapy trials.

1.3 Background to the study: cell therapy trials in context

The following overview of translational cell therapy research looks first at the current position in terms of basic scientific research, and then explores how this relates to the development of clinical applications. It draws on and synthesises key literature from across the disciplinary spectrum and is intended to serve a number of important purposes. Firstly, it locates my work within the wider academic discussion on cell therapies, and thus demonstrates how it was shaped by and what it adds to these debates. Secondly, it provides important factual information about cell therapies, which will be necessary for any reader unfamiliar with the field to fully understand the remainder of the thesis. Thirdly, and perhaps most importantly, it elucidates the key issues and themes that, in conjunction with the theoretical framework I have already discussed, informed the framing of my research questions, which are detailed at the end of this chapter.

1.3.1 Scientific research - the view from the bench

In the scientific literature, stem cells are typically defined as undifferentiated cells which have the capacity for self-renewal and can differentiate into different cell types (see for instance Bajada et al., 2008). Stem cells are typically categorised based on their potential for differentiation, e.g. multi- or pluri- potent, and/or their source, e.g. embryonic stem cells, blood stem cells, neural stem cells etc. The term 'stem cell research' is perhaps most commonly understood to refer to pluripotent cells, and it is certainly here that there has been most expectation of developing genuinely revolutionary therapeutic applications (Murry and Keller, 2008). Pluripotent cells have the ability to differentiate into any cell in the human body, and will self-renew indefinitely in culture (Graf and Enver, 2009). Despite often being referred to as embryonic cells, there are now in fact two potential sources of pluripotent cells: human embryonic stem cells (hESCs), which can be isolated from the inner cell mass of a human blastocyst (using either naturally fertilised embryos or somatic cell nuclear transfer), and induced pluripotent stem cells (iPSCs), which are terminally-differentiated or 'adult' cells that have been reprogrammed to a pluripotent state.

HESCs were first isolated in 1998, and at least 225 lines have now been developed (Bajada et al., 2008). Isolating embryonic stem cells requires the destruction of a human embryo, making hESC research one of the most ethically challenging areas of stem cell research, but scientific research on hESCs is growing both in terms of output and geographical spread (Ben-David et al., 2012). The main issue that will need to be addressed in order for the therapeutic potential of hESCs to be realised is the risk of tumour development due to undifferentiated cells being implanted, and the fact that differentiated cells may retain some epigenetic properties of the original cells (Lysy et al., 2012). There is also a concern about the genomic instability of hESCs in culture, and continuing uncertainty around their immunogenicity (Ben-David et al., 2012).

IPSCs offer an alternative that could overcome the ethical and immunological challenges of embryonic cells. There has been significant progress in the basic science in the decade since the process for creating iPSCs was first

published (Takahashi and Yamanaka, 2006; Yamanaka, 2012), and the first clinical trial using iPSCs was approved in 2013 (Li et al., 2014). Overall understanding of the process is still in its infancy, however, and there are many hurdles to overcome before widespread clinical application becomes a realistic possibility (Jopling et al., 2011). Firstly, the reprogramming process is extremely inefficient, with typically only 1% of cells being reprogrammed, and the outcome of the process appears to be highly dependent on micro-environmental conditions within the lab, all of which would cause significant manufacturing challenges in a clinical context (Yamanaka, 2012). Secondly, the reprogramming process itself appears to increase the tumorigenicity of the cells (Daley and Scadden, 2008), and also exposes them to stress, which selects for cells where the stress response gene is mutated, making them potentially more susceptible to tumour formation than hESCs (Jopling et al., 2011; Ren et al., 2012). The scale of the challenges facing iPSC treatments was underlined by the fact that the first trial had to be temporarily suspended due to mutations being detected in the cells (Scudellari, 2016). It may be that for the foreseeable future their use in clinical research will be limited to providing 'disease in a dish' models for drug toxicity testing, rather than widespread clinical trials.

Also known as 'somatic' or 'adult' stem cells, multipotent stem cells reside within the adult body, and are involved in the regeneration and repair of specific tissues. Unlike pluripotent cells, they are not thought to have the ability to differentiate into any cell in the human body, but can differentiate into specific cell lines within their germ layer. The properties and behaviour of multipotent stem cells are largely determined by the surrounding microenvironment, or niche, and much recent scientific research has focussed on better understanding how the niche affects stem cell proliferation, and how these mechanisms could be manipulated for clinical purposes (Jopling et al., 2011). Four main types of multipotent cells are currently being researched with a view to clinical applications: hematopoietic, mesenchymal, limbal and neural cells. These cells are generally thought to pose a lower risk of teratoma formation due to their lower capacity for differentiation (Colman, 2008), and offer the opportunity to

develop autologous treatments (i.e. using the patient's own cells), thus avoiding the issues with immune response faced by pluripotent cell treatments (Daley and Scadden, 2008). Multipotent cells also raise no specific ethical issues, as they are not derived from embryos (Lo and Parham, 2009). These factors make multipotent cells much less problematic than pluripotent cells for both scientific and clinical research, and many commentators believe that they are therefore likely to reach the clinic first (Colman, 2008; Ren et al., 2012). The clinical potential of multipotent stem cells is also dependent on a number of other factors, including how easy the cells are to harvest, how effectively they can be expanded in culture, and how easily they can be transplanted to the desired treatment site.

The categorisation of stem cells that I describe above is useful for gaining a broad understanding of the scientific and clinical position, but it is far from precise or consistently applied. For instance, the term 'embryonic' is often used as synonymous with 'pluripotent', whereas in fact pluripotent cells can be derived from sources other than a developing embryo. Likewise, the cell source does not necessarily definitively specify the cell type - for instance, bone marrow-derived cells might refer to mesenchymal stem cells, hematopoietic cells or a mixture of a variety of cells.[2] The term 'stem cell' itself is frequently used in the media, academic literature and policy and legal documentation without question or clarification, suggesting that the term refers to an object whose definition is fixed, uncontested and universally understood. However, recent scientific research suggests that the biological properties of stem cells, such as their potency or proliferation potential, are in fact not fixed at all, but are dependent on a number of interdependent variables such as developmental stage, cell cycle and environmental factors. For example, the fact that different adult cells require different transcription factors for reprogramming into iPSCs suggests that some adult cells may be 'closer' to pluripotency than others, and the differential rate at which cells of the same type become reprogrammed suggests that the cell

[2] In the interests of brevity, and clarity, I have largely skimmed over the complexity and imprecision of stem cell terminology in this brief introductory literature review, however I examine this issue in much greater detail later in the thesis.

cycle may also be linked to potency (Jopling et al., 2011). Other findings that tend to support this view are the change in proliferation potential between foetal and adult MSCs, the heterogeneity seen in base populations of adult HSCs (Copley et al., 2012), and the significant effect of laboratory processes on the production of iPSCs (Yamanaka, 2012).

This fluid biological picture has led some social scientists to question the conception of 'stem cells' as discrete and unchanging physical objects. For instance, Geesink et al. (2008) suggest that stem cells should not be considered as a distinctive category of cells, but rather should just be seen as cells at a particular stage in a process. Eriksson and Webster (2008) take this one step further, questioning whether stem cells should be considered as *objects* at all, or whether in fact it is the *process* that defines the characteristics of the cell. This is not necessarily a new idea in the scientific sphere: as long ago as 1997, questions were raised in the scientific literature suggesting that rather than being a fixed property, 'stem-ness' should be conceived as a 'spectrum of possibilities' that can only be uncovered by experimentation (Cooper, 2006). Scientifically, then, stem cells cannot be conceived of as one-dimensional physical objects, but rather must be considered in three dimensions: physical, spatial and temporal. This has significant implications for the therapeutic application of stem cells, particularly for transplantation, because the cells introduced into the body are not fixed entities and so may change over time, or when exposed to a novel niche *in vivo*.

The past two decades have seen significant progress in scientific stem cell research, including the cloning of Dolly the sheep in 1997, the isolation of hESCs in 1998, the development of iPSCs in 2006, and human somatic cell nuclear transfer in 2013. There have also been false starts, of course, such as the Huang scandal in 2005, and wrong turns, such as pursuing the theory that MSCs could become pluripotent when exposed to a different niche (Daley, 2012). Nevertheless, the tone of the scientific literature is generally one of enthusiasm and progress, for instance the swift development of the cell reprogramming process which can be seen between the initial paper on iPSCs published in 2006 and the update in 2012 (Takahashi:2006hi and Yamanaka, 2012 respectively).

Review papers covering the translation of these breakthroughs into clinical applications, however, tend to be much more cautious, highlighting the moderate or non-existent clinical success so far, focussing on the challenges to be overcome and setting the bar high for stem cell therapies by pointing out the success rate achieved by other treatment regimes. For instance, Lindvall (2012) notes that scientific breakthroughs have not so far led to useful stem cell treatments for CNS disorders, Wainwright et al. (2006) report that scientists are sceptical of developing even experimental embryonic stem cell treatments for diabetes in the near future, and Daley (2012) argues that other than hematopoietic stem cell (HSC) transplantation, all stem cell treatments are essentially experimental.

Some commentators argue this means that regenerative medicine has so far failed in its aim, or suggest that, for the present, stem cell therapies can only be realistically seen as a 'heroic' last resort (Daley, 2012; Weissman, 2012), which should only be explored for diseases where risks are high and there are no other treatment options - for instance Huntingdon's disease but not Parkinson's (Lindvall, 2012). Clearly, this is a far cry from the rhetoric of 'regeneration' and 'cure': the anticipated future where ageing is reversed and chronic diseases such as diabetes and Alzheimer's are cured (Cooper, 2006). This gap between rhetoric and current scientific reality creates the sense that stem cell research, like pluripotent cells themselves, is defined by its 'not-yet-ness' (Eriksson and Webster, 2008). To understand the reasons for this it is necessary to explore the dynamics of stem cell research as a clinical field rather than simply a scientific endeavour, and to understand the technical and societal issues that mediate between basic science and clinical application.

1.3.2 Clinical research - the journey to the bedside

Bringing cell therapies to the clinic relies not just on scientific breakthroughs, but also on these breakthroughs being developed into effective, affordable clinical treatments. The majority of clinical cell therapy research has focussed on transplantation, i.e. the temporary or permanent engraftment of introduced cells into target tissue (Miller and Kaplan, 2012). The key concern for transplantation-based therapies is the risk of tumour formation, and the scale of the risk is linked

to the potency of the cells (undifferentiated cells being more likely to become cancerous). This makes it important to control the variability of cells used for transplantation, which can be difficult both in terms of the inherent variability of stem cell populations, and because of further variability introduced by laboratory processes.

Transplantation-based treatments can use either autologous (patient's own) or allogeneic (donor) cells. The most appropriate source of cells depends on a number of factors, including the type of disease being treated, ease of obtaining donor cells, and number of cells required for treatment. For autologous treatments, it will often be a challenge to source enough healthy cells, the process for harvesting them could introduce additional trauma, and the cells transplanted will be genetically identical to those being replaced, so may be prone to the same problems causing disease in the first place (unless some genetic modification is undertaken). This makes allogeneic treatments an important alternative, but these encounter immune response problems which will have to be overcome if 'off-the-shelf' products are to become a reality (Daley, 2012). Various ways of addressing this issue are being explored - for instance, one potential solution for diabetes treatments is a method of encapsulating the transplanted cells, so they can perform their basic function but not allow the diffusion of larger molecules, cells, or antibodies which would trigger an immune response (Lysy et al., 2012).

In addition to engraftment, another potential mode of action involves harnessing the immunological, anti-inflammatory and/or trophic properties of certain cells. These treatments, which can be allogeneic or autologous, involve introducing cells systemically to prompt particular actions in the body, rather than transplanting them to replace or enhance tissue - for instance, the use of systemically introduced HSCs to 're-set' the immune system in treatments for MS (Franklin et al., 2010). In contrast to cell transplantation, which is often positioned as being akin to organ transplantation, systemic cell therapies may have more in common with the pharmaceutical treatment model, in that the cells are not intended to remain in the body. These treatments may therefore be

comparatively less risky than transplantation, however the benefits are also potentially less dramatic. For instance, evidence from both animal models and clinical trials using MSCs suggests that the therapeutic effects generated by such treatments may be transient (McNiece, 2012). Also, the availability of drugs that can achieve similar effects means that the relative risks and benefits of this type of cell therapy need to be carefully considered (Lindvall, 2012). Understanding of the exact mechanisms through which these treatments work is currently limited, making it difficult to gauge how effective they could be, and the level of risk they pose (Daley, 2012).

Both transplantation and systemic application present plausible clinical applications for cell therapies, however real breakthroughs in clinical cell therapy research have so far largely been limited to animal models, and HSC transplantation is currently the only cell therapy in widespread clinical use (Daley, 2012). There are indications that clinical research is gathering pace (Li et al., 2014), but the majority of trials are still in the early phases. High profile failures in later-phase trials, such as two trials of foetal neural cell transplantation for Parkinson's Disease (Ishii and Eto, 2014), have dampened optimism in some clinical areas. Furthermore, the majority of trial activity involves established treatments - i.e. HSC transplants for existing indications - with only a very small proportion looking at tissue regeneration, and an even smaller number using pluripotent cells (Foley and Whitaker, 2012). It is also notable that the majority of registered trials are clinician-led and use autologous cells, which, as discussed above, are inherently lower risk but also have lower potential for revolutionising patient care.

To understand why advances in scientific knowledge have not necessarily led to corresponding advances in the clinic, it is necessary to examine the complex interactions between science, technology and society. Salter (2013) describes a 'triangle of tensions' facing innovation in health technology: "the science may prove inadequate, society unsympathetic or the market unwilling." Below, I consider how these three tensions have affected the development of cell therapies, providing an insight into the challenging environment in which cell therapy trials take place.

Science inadequate

The previous section of this chapter touched on a number of basic scientific issues which are currently perceived as hindering the development of effective stem cell therapies. Some of these issues are relatively well-defined, such as the need to improve the process for reprogramming iPSCs to reduce the risk of tumour formation, or to better understand the immunogenicity of hESCs. Although such well-defined problems cannot yet be overcome, their parameters are broadly understood, and they can be addressed using well-established scientific experimental techniques. These 'known unknowns' (Eriksson and Webster, 2008) can therefore to some extent be considered practical problems, and it could be expected that progress in these areas will be relatively linear, such as the process of incremental discoveries described in Yamanka's 2012 paper detailing the progress made with iPSCs. Progress in the lab, however, does not necessarily lead to progress in clinical understanding. This is due in no small part to the fact that animal models, which are used extensively in the basic scientific research, have limited application to human physiology and disease. For instance, the model used to test Parkinson's Disease in mice is very different from the human disease (Lindvall, 2012), and the safety of iPSCs cannot be proved through mouse models alone (Yamanaka, 2012). This means that although laboratory research can greatly advance our understanding of how stem cells behave in a petri dish or in an animal, it is much more difficult to research how they behave in a living human body.

As well as these relatively well-understood practical issues, there are other aspects of the basic scientific research that present what might be termed more epistemic challenges for translational stem cell research. A good example of this is the changing consensus on the properties of MSCs, which were originally thought to be multipotent, then for a time appeared to have pluripotent capabilities, and are now generally accepted as being multipotent again. These fundamental shifts in scientific understanding, or 'unknown unknowns' (Eriksson and Webster, 2008), are unlike the practical problems described above. They are largely unpredictable, and therefore potentially much more disruptive, and they

mean that progress in the basic science of stem cells is far from linear. This is not unusual, or necessarily unwelcome, in the scientific world, but presents a challenge for clinical translation because a fundamental change in scientific understanding of stem cell properties can also significantly alter the likely clinical potential of those cells. Clinical research, however, is often not able to adapt quickly enough to keep up with the pace of change in the basic science, demonstrated by the continuation of trials based on out-dated understanding of the properties of MSCs (Bianco et al., 2013b). There is therefore a fundamental tension between the time needed to sufficiently develop the basic scientific knowledge base, and the societal push to develop clinically useful and commercially viable treatments.

Scientific unknowns (whether known or unknown) can be understood as the current limits of scientific *understanding*, and there is an unspoken assumption in the scientific literature that the challenges they pose will eventually be overcome through the acquisition of sufficient knowledge. It is also possible, however, that barriers to clinical translation may stem from limits to scientific *possibility*: that is, regardless of any progress in scientists' ability to manipulate cells, it may simply not be possible to treat certain disorders in the way suggested by the hype around regenerative medicine. For some scientists, biology itself (i.e. the inherent characteristics of cells and the bodily systems they aim to treat) potentially imposes finite boundaries on the clinical potential of stem cells (Wainwright et al., 2006). For instance, both Lindvall (2012) and Daley (2012) question whether regeneration of the central nervous system will ever be possible, because it is a complicated and interconnected system created by a "highly complex choreography" during foetal development, which would be very difficult to replicate in adults. Inherent biological limitations may also be a factor that will determine whether it is possible to overcome two of the most important clinical obstacles for cell therapies: the risk of tumour formation presented by pluripotent cells, and the immune response issues associated with allogeneic treatments.

As well as challenges relating to the underlying biology of stem cells, and the limits of current (and possibly future) scientific knowledge, there are also a number of more technical issues that will need to be overcome in order for it to be practical to use cell therapies in the clinic. Perhaps the most important issue concerns the need for large scale production of consistent batches of cells, which presents a considerable logistical challenge. Mass production of human cells is a much greater challenge than mass production of drugs or biopharmaceuticals, because the human cell is a complex living organism rather than a relatively simple protein (Mason and Dunnill, 2007). Small variations in the laboratory environment or culturing process can have a significant impact on the resulting cell populations (Eriksson and Webster, 2008; Yamanaka, 2012), making it difficult to ensure consistent results when production takes place in more than one location. Furthermore, the manufacturing process for cellular products is currently very labour intensive, which is expensive and creates the risk of errors and inconsistencies (Foley and Whitaker, 2012). To add an additional complication, it is not even necessarily clear that consistency in cell batches is desirable. The inherent heterogeneity in stem cell populations, and the growing understanding of potency being a stage rather than a state, suggest that some level of heterogeneity may be integral to the 'stem-ness' of the cell. Thus, achieving complete consistency may actually reduce or even eliminate the therapeutic potential of the cells.

Effective mass production of cell therapies will clearly require a better understanding of the impact of the production process on the quality of the resulting therapeutic product (Mason and Dunnill, 2007; Foley and Whitaker, 2012). However, there is currently no consensus about how to measure the characteristics and quality of clinical-grade cell batches. For instance, no one marker has been discovered that can be used to identify hESCs (Eriksson and Webster, 2008), and Yamanaka (2012) reports so much cross-over in the markers used to test hESCs and iPSCs that it is not possible to use markers alone to distinguish whether two populations were different cell types, or the same cells simply produced in different labs. The agreement of standard markers for

identifying clinical-quality cells will be an important factor in the clinical translation of stem cell science. However, although the first steps are being taken, it is difficult for these discussions to keep pace with scientific advances in the field (Mason and Dunnill, 2007). Like so many of the problematic aspects of cell therapy translation, the development of standards is clearly not only a technical concern, but also a social one (Webster and Eriksson, 2008).

Society unsympathetic

Using stem cells for biological or clinical research raises a number of ethical issues, perceptions of which differ both geographically and politically. The interaction between these different ethical responses is a significant factor in shaping cell therapy research and commercialisation globally. One of the most important ethical considerations is the creation and/or destruction of human embryos for research purposes, which is required for isolating hESCs (Prainsack et al., 2008; Lo and Parham, 2009; Sleeboom-Faulkner, 2008). Another factor that complicates embryonic research is the need for donated embryos or oocytes. Donating oocytes is invasive and presents some medical risk to the woman, and raises significant issues surrounding informed consent and financial compensation/incentivisation (Schultz and Braun, 2013). Egg sharing during IVF, like the use of unused embryos from IVF cycles, is arguably less problematic, as it does not expose women to additional physical risk, however it raises similar concerns about consent and financial incentives (Lo and Parham, 2009). These ethical issues largely affect basic scientific research, as they relate to the process of sourcing embryonic cells for research purposes. However, they can also feed through into clinical trials - for instance, donated oocytes are used to create allogeneic embryonic stem cell lines for clinical use.

There are also specific ethical considerations that arise directly from the clinical use of stem cell therapies, particularly when these therapies are experimental. Lo and Parham (2009) highlight the problematic nature of informed consent for clinical trials of stem cell therapies, given the complexity and uncertainty of the underlying science. They also raise the concern that properly informed consent for stem cell trials must include a wider range of factors than

for more conventional treatments. For instance, an individual patient may wish to avoid having cells implanted that were sourced from an embryo, so the information provided before consent must be sufficient for them to make an informed choice on ethical as well as medical grounds. Linked to the issue of informed consent, there is also the possibility of patients agreeing to take part in trials under the misconception that these experimental treatments offer a genuine possibility of curing them. These expectations may be out of step with reality, as early trials are only intended to assess safety, and even in later efficacy trials many treatments do not prove any better than existing options (Lo and Parham, 2009). Although this therapeutic misconception is to some extent an issue with all clinical trials, it is likely to be particularly prominent in trials of stem cell treatments, where expectations have been raised by the promise of revolutionary treatments that will cure disease and reverse ageing (Cooper, 2006), and which aim to treat severe and debilitating conditions for which patients often have no other treatment options.

Alongside, and linked to, these ethical constraints, cell therapies have also been affected by an increasingly cautious approach to regulation, which has particularly limited clinical research of the most experimental therapies. Gaining approval for large Phase 3 trials, especially those using pluripotent cells, has required "herculean effort" (Daley, 2012). For instance, Geron's application for a trial of an hESC therapy for spinal injury ran to between 20,000 and 30,000 words (Parson, 2008). The perception of pluripotent cells being high risk also affect trial design, with strict exclusion criteria being required to minimise risk and maximise the chance of seeing benefit (Foley and Whitaker, 2012). Differing trial requirements between member states have also been a complicating factor for cell therapy trials in the EU, although steps are being taken to improve the efficiency of the process (NHS European Office, 2014). Because of the costs and time involved in undertaking full-scale clinical trials, there has been a focus on treatments for orphan diseases, which have less stringent requirements as well as longer patent protection on approved products (Haddad et al., 2013). Much clinical development is also carried out under the 'Hospital Exemption', which

provide a less onerous regulatory framework for individual clinicians using experimental treatments on a patient-specific basis (Faulkner, 2009; Foley and Whitaker, 2012). Nevertheless, lack of flexibility in trial regulations, particularly in early-phase trials, and the onerous demands placed on researchers to demonstrate safety prior to trial approval, are still perceived by many in the industry to be a significant barrier to the successful development of cell therapies.

Market unwilling

Ethical issues can directly affect cell therapy innovation by delineating the scope of acceptable research, and can also play a more indirect role by affecting the funding available for that research. This phenomenon was particularly visible under the Bush administration in the US, when federal funding could not be used for research using embryonic stem cells (Lo and Parham, 2009). The regulatory framework can also have an indirect impact on innovation, for example by affecting the relative financial viability of research in different areas, or the commercial potential of the treatment being researched. Indeed, financial considerations can often outweigh scientific and clinical factors in shaping the direction of translational research. This was the case when the prohibitive costs of running Phase 3 clinical trials led to one clinic changing the primary target indication for one of its treatments, not because this was the area of greatest clinical need, or the most likely to be successful, but in order to gain orphan indication status and reduce the cost of the trial (Haddad et al., 2013). Another example is Geron's surprising decision to withdraw from embryonic stem cell research shortly after gaining approval for the first hESC trial, which was partly motivated by the regulatory and ethical problems associated with the field (Sukkar, 2011). Given that the initial approval for the trial was seen as a ground-breaking moment, this withdrawal had great symbolic impact within the industry - particularly because, in the absence of public funding for stem cell research in US at the time, it was Geron who funded the initial scientific research which isolated hESCs (Cooper, 2006).

A challenging regulatory environment is not the only factor that has constrained funding for clinical stem cell research. During the early years of tissue engineering, translational research was largely commercially-funded, but disappointing therapeutic success led to a withdrawal of that support (Kemp, 2006). Since 2008, this funding gap has been exacerbated by the global financial recession, and securing funding for research, in particular for large confirmatory trials, is now a significant problem in the sector (Morrison et al., 2013; Weissman, 2012). Part of the reason funding is so problematic is that the time to market for cell therapies is expected to be longer than for more conventional treatments, making it difficult to secure venture capital funding (Colman, 2008; Morrison et al., 2013). This issue has also deterred significant investment from the big pharmaceutical companies, who are also concerned about the business model for scaling up and commercialising cell-based treatments, and about the ethical implications of hESCs (Wainwright et al., 2008). There is also uncertainty about the extent to which products based on embryonic cells will be patentable, and therefore profitable. Various countries have used patent law in an attempt to restrict the commercialisation of embryonic stem cells, however the language used in these laws is (perhaps deliberately) vague. Thus, instead of creating greater clarity they have in reality led to a great deal of uncertainty as to what is and isn't legal and/or patentable (Cooper, 2006; Bonetta, 2008). Differences between laws in the US and the EU, and inconsistency between European states in terms of how they have applied the law, introduce additional complexity, as research that may be legal or patentable in one state may be illegal in another (Bonetta, 2008).

In summary, then, the translational environment for cell therapies is characterised by a number of scientific challenges, considerable ethical issues, a complex and prohibitive regulatory framework, and significant funding constraints. These issues are relatively well-established in the literature, as is the fact that clinical trials of cell therapies present specific methodological, practical and financial challenges. To date, however, there has been no detailed examination of the role that clinical trials play in the translational process for cell

therapies, and the extent to which the challenges they pose have shaped and constrained innovation. By putting trials 'under the spotlight' so to speak, this thesis will examine the wider challenges facing the field, and explore how trials could be used to overcome rather than add to these challenges. The research aims, and the specific research questions addressed, are drawn from the literature reviewed above, and I will now go on to explain how these questions were developed, and how they are addressed throughout the thesis.

1.4 Research questions

RQ1 - How might the UK cell therapy trials landscape be characterised?

One of the ways in which STS can make a valuable contribution 'in the policy room' is by characterising and anticipating an emerging field (Webster, 2007), and in particular by highlighting ways in which conventional understandings of the field may not align with the reality of day-to-day practice. Thus, the first task for my study was to characterise the cell therapy trials landscape in the UK, both by mapping trends in trial activity and by exploring the policy, institutional and social contexts in which these trials take place. This question is first addressed in Chapter 3, which explores the regulatory and policy environment for cell therapy trials in the UK, and details the characteristics of trials currently underway. The picture that emerges from this analysis is of a small, heterogeneous and fragmented field, suggesting it may not be valid to consider cell therapy trials as a homogenous group (as much of the policy and academic literature does). Other aspects of cell therapy trials, such as the distinction between allogeneic and autologous cells, are also shown to be more complex, and perhaps less useful as analytical categories, than the literature might suggest.

This characterisation of the field also elucidates a key tension at the heart of cell therapy translation, which is the disconnect between the regulatory and policy environment - which is aligned with a commercial development/innovation model - and the fact that the majority of trialling is actually taking place in the academic sphere. This issue is expanded upon in Chapter 4, which characterises the social dynamics of the trials landscape by examining the role of, and interaction between, the three key actors involved in trials: clinicians, companies and patients. This analysis

highlights the tensions between the clinical-academic model of innovation and the commercial realities of the field, and in particular the problems caused by the fact that many of the individuals and institutions running cell therapy trials lack experience in trialling medicines. Chapter 4 also explores another key tension in the social dynamics of trials, relating to the extent to which patient agency can or should be accommodated. This presents distinctive challenges in terms of informed consent, therapeutic misconception and the evaluation and prioritisation of acceptable risk vs. likely benefits.

RQ2 - What challenges are faced in the day-to-day running of cell trials?

Clinical trials have been raised as a particular challenge for regenerative medicine in both the policy and academic literature, and these commentaries suggest some specific aspects of trials that may be problematic for cell therapies (such as methodological issues, financial constraints and practical challenges). However, there is no detailed analysis of how these challenges are experienced in, and affect, the day-to-day work of trialling. Furthermore, it is not clear to what extent these challenges are unique to cell therapies, and also how much they relate to any use of cells in the clinic, rather than the clinical trial *per se*. Will and Moreira (2010) argue that the tensions and practical challenges inherent within the research process are a crucial factor in the development of new ways of thinking, suggesting that "understanding the political and economic contexts in which clinical trials are conducted and reported should help identify creative approaches to knowledge governance." With this is mind, Chapter 5 examines the challenges involved in trialling cell therapies in some detail, with a view to understanding how these might impact on innovation and knowledge governance. This analysis demonstrates that many of the day-to-day challenges experienced are logistical and locally-contingent in nature, and in particular relate to the length of time it takes to undertake a trial, the logistics and unpredictability of working with cells, problems with funding for trials and reimbursement for the treatment, and the number of different professional domains that must work together effectively for the trial to work.

RQ3 - How is uncertainty understood and managed in cell therapy trials, and how does this relate to uncertainty in the underlying science?

As I discussed earlier in this chapter, one of the most difficult challenges facing translational cell therapy research is the significant uncertainties that remain as yet unresolved, some of which are well-understood ('known unknowns') and others which cannot be predicted ('unknown unknowns'). Thus, an in-depth understanding of the different types of uncertainty involved in cell therapies, and the extent to which trials play a role in resolving them, provides a useful framework for understanding how trials contribute to the innovation process. This also provides an opportunity to explore the various ways that uncertainty, ignorance and indeterminacy are constructed and deployed by different actors involved in cell therapy trials, and how the new uncertainties created by this emerging technology are reconciled in practice. Chapter 6 explores this issue by examining both scientific and clinical uncertainties, and the ways in which these uncertainties interact during trials. This analysis demonstrates that although clinical trials are a vital means of resolving both scientific and clinical uncertainty, the linearity of the trialling process and the rigidity of trial protocols can be problematic for innovation, which is a recursive process that requires uncertainties to be resolved in an iterative, contextualised way.

RQ4 - How is evidence conceived and used by the different stakeholders involved, and what implications does this have?

The epistemic critiques of EBM, and Jasanoff's idiom of co-production, suggest that it is important to consider the role of the evidence in cell therapy trials, and how this evidence is understood and mobilised by different stakeholders in the field. This allows us to widen the scope of our inquiry, looking not just at individual trials but also at how knowledge governance structures, and in particular the specific conceptualisation of evidence promoted by evidence-based medicine (EBM) and encoded in the randomised controlled trial (RCT), interact with the innovation process. By taking this more macro view we can also extend the analysis of social dynamics which began in Chapter 4, by exploring the institutional context in which evidence is evaluated and decisions get made. In Chapter 7, I examine how different actors in cell therapy trials conceive of and use evidence, and in particular how the

idea of the RCT as the 'gold standard' for evidence in healthcare holds up in the context of cell therapy trials. This discussion suggests that although the supposed objectivity of the method is valued in principle by both trialists and decision makers, the complexity of cell therapies creates significant contingency surrounding trials, suggesting a flexible and nuanced approach to evidence is warranted. In the concluding chapter of the thesis I discuss how this might be achieved and make some recommendations for the field, and also consider my findings in the light of the theoretical framework I set out earlier in this chapter.

2. Methodology and Methods

In line with the conceptual framework I set out in the previous chapter, my methodological approach situates trials not as a 'gold standard' of generating evidence in healthcare, but as a social process that both shapes and is shaped by the day-to-day work of scientific and clinical practice. In the specific context of cell therapies, trials take place at the intersection between science and the clinic and are thus integral to the process of 'translation' in bio-medicine, and the co-production of social order around this. Following the co-production idiom and the wider STS traditions it draws from, my methodology thus focuses on the 'doing' of trials. In particular I was interested in exploring the various interactions involved in the trialling process - for instance between different social actors, between institutions and individual actors, between professions and academic disciplines and the identities they adopt, between material objects and their social constructions, between different representations of cell therapies and identities, and between trial protocols and day-to-day practice on the ground. My methodology thus focusses on interrogating these various interactions with a view to understanding how they result in new forms of practice, new understandings of patients and disease, and new forms of social order.

Situating trials in this way allows me to interrogate the field in the context of the ontological position I set out in the previous chapter - not adopting a purely realist or relativist approach to materiality, but rather looking at the relationship between reality and our understanding of it. In order to do so I adopt an epistemological position that reflects this, and also aims to balance the different expectations of the disciplinary audiences I am addressing. Biology and the health sciences tend towards a positivist view of knowledge, in that they assume a fairly straightforward relationship between the world and our perception of it (Lyle, 2016). STS research, on the other hand, has tended towards a more constructivist perspective (Sismondo 2009), holding that there is no singular underlying 'truth' that can be uncovered through research, but rather that our ways of knowing the world are mediated by social factors and are always contingent and provisional. At their

extremes neither of these positions is appropriate for my research - a simplistically positivist analysis would not be aligned with my conceptual framework, but extreme constructivism would be ill-suited for a study that aims to be relevant and credible to a scientific audience, and to attend to and suggest solutions to the concerns of those working within the field itself. Given this, my approach has been to be attentive to and reflect the epistemic and practical concerns of stem cell scientists, while doing so in the context of (co)production. This approach echoes the notion of 'contextualism', which "retains an interest in the truth which constructivism rejects, but still sees knowledge as emerging from social contexts and reflecting the researcher's position" (Clarke and Braun, 2013, p.30). This epistemological position underpins my methodological and analytical approach, which I set out below, and then informs my choice and use of research methods, which are detailed in the second part of this chapter.

2.1 Methodological and analytical approach

Three key considerations influenced my methodological approach. Firstly, the methodology needed to align with my ontological position (a balance between realism and relativism) and my epistemological stance (which is concerned with the 'truth' but recognises the importance of context in our understanding of it). Secondly, the methodology needed to be able to address the research questions and also the orientation of the study as broadly problem-focussed and the overarching aim to contribute to a 'serviceable' STS. Thirdly, although incorporating interdisciplinary elements the methodology needed to be located within the broad boundaries of sociological research, both because this is where the thesis would be examined and also because my background and research training is in social science. I decided to adopt a mixed-methods approach for all of these reasons. Mixed methods are often used in interdisciplinary research, in part because they offer the flexibility to adapt to different disciplinary expectations and allow for different ontological and epistemological perspectives to be incorporated.

Alexander and colleagues (2008) describe a number of reasons for using a mixed methods design, including triangulation, complementarity, development,

initiation and expansion. The main benefit for my own study was *complementarity*: i.e. I used multiple methods not to in order to obtain a more 'accurate' picture of a singular reality, but rather to "reveal the different dimensions of a phenomenon and enrich understandings of the multi-faceted, complex nature of the social world" (Alexander et al., 2008, p.218). My mixed-methods design was also motivated by *expansion*, meaning mixed methods can be used to address a wider range of research questions than a single method. In the case of my own study, for instance, I was able to characterise the field using quantitative methods and qualitative data from interviews, and also to understand the day-to-day challenges experienced though direct observation. Another secondary benefit of using mixed methods was *initiation*, whereby puzzles that appear in one part of a study can be explored in other parts using different methods. In my case this was particularly apparent during the planning of my research, when I started to encounter the 'puzzle' of how the field of cell therapy trials is defined (which I expand on below in the discussion of the construction of the trials dataset). This initial puzzle led me to incorporate a quantitative characterisation of the field in addition to the planned qualitative work, and this quantitative analysis then threw up further 'puzzles' that I explored in subsequent qualitative fieldwork and analysis.

Although the term mixed methods is often used to refer to research that uses both qualitative and quantitative methods, mixed-methods designs can in fact use only one or the other (Alexander et al., 2008). In fact, it has been argued that qualitative and quantitative research represent fundamentally different epistemological positions, or different paradigms, and thus adopting both in the same study cannot be justified (Spicer 2018). Others, such as Bryman (2012, 1992) see them rather as different approaches to social research, associated with a certain collection of methods. For Bryman these different approaches are influenced by different epistemological positions but not defined by them, thus they "can have and do have an independence from their epistemological beginnings" and can therefore justifiably be combined in one research design. There are a number of ways in which qualitative and quantitative research can complement each other that had benefits for my study (Bryman 1992). Firstly, quantitative data can facilitate qualitative

research - for instance, the construction of a quantitative dataset helped to define the scope of my qualitative research, and also provided a sample frame for the interviews. Secondly, they provide complementary strengths in terms of understanding both structure and process. Quantitative analysis is useful for describing structural features and qualitative analysis is better suited to understanding processual features, both of which are important in analysing concepts such as style of practice and co-production. Thirdly, the use of both helps to address the problem of generality, because the addition of some quantitative evidence helps to mitigate the fact that it is hard to generalise the findings from qualitative research. This was particularly important in developing recommendations that would be applicable for the whole field, and was also necessary for the findings to be seen as credible and relevant in biology and health sciences, where there is often an expectation that research will be generalisable. Fourthly, qualitative research helps to facilitate the interpretation of relationships between quantitative variables, which was helpful in challenging conventional representations of the field and proposing a more nuanced, contextualised understanding. Finally, the relationship between the macro and micro can be better interrogated using both methods, because quantitative research taps into the large-scale, structural features of social life, whereas qualitative addresses the small-scale, behavioural aspects. This is very useful for a study that aims to interrogate the relationship between the day-to-day work of individual trials and the broader translational and knowledge governance frameworks that these trials are part of.

Mixed methods can relate to either the methods of data collection, the analytical approach, or both (Alexander et al., 2008, p.218). My methodology used a mixture of data collection methods which I will discuss in more detail later in this chapter, but briefly they included interviews, observational research and analysis of documents and other secondary data. All these methods could potentially generate both qualitative or quantitative data, and thus could be analysed in more than one way. I undertook two types of analysis: firstly, I constructed a dataset of UK trials which I analysed quantitatively using descriptive statistics; and secondly, I analysed the interview transcripts, field notes and other documents and sources using

qualitative thematic analysis. When such a mixed methods design is used the different elements can either be given equal weighting or more emphasis can be placed on one or the other, so it is important to clarify the relative status of the different methods used (Alexander et al., 2008, p.218). In keeping with the fact that this study leans towards constructivism, but with the aim of also incorporating a realist perspective, the emphasis is on the qualitative aspects of the analysis with the quantitative analysis playing a secondary role. In the qualitative analysis the interviews and observational research are given equal weighting, although they do of course have different epistemological assumptions and address slightly different issues, which I discuss further below.

I will detail the quantitative analysis of the dataset when I discuss the specific research methods later in this chapter, but as the qualitative analysis represents the primary focus of the thesis I will explain my overall approach to it here, before providing more detail pertaining to specific research methods in the relevant sections. I analysed qualitative data using thematic analysis (or thematic content analysis), which unlike other techniques such as grounded theory or Interpretative Phenomenological Analysis (IPA) is solely a method of data analysis and is not linked to a particular theoretical approach (Clarke and Braun, 2013, p.174). As such it is flexible in terms of ontological and epistemological positions and approaches to data collection, and was thus well-suited to the needs of my study. Thematic analysis has been criticised for resulting in purely descriptive accounts of qualitative data, however it can be taken further to identify and interrogate underlying themes (Rivas 2018), and this is the approach that I aimed for. The analytical process is similar to other techniques such as grounded theory and IPA, but there are important differences between them which directed my choice towards thematic analysis. Firstly, although their coding processes are similar, thematic analysis focuses on what a phenomenon 'looks' like to the individuals (their lived experience) whereas IPA is more concerned with what it 'feels' like (Rivas 2018). Given my research aims to uncover the different perspectives, experiences and interactions involved in trials a focus on lived experience seemed most appropriate. Secondly, although grounded theory uses thematic analysis in the early stages it then goes on to develop abstract

concepts from the themes and build up theory from the concepts (Rivas 2018). Being a largely problem-focussed interdisciplinary study, the production of discipline-specific outcomes was of secondary importance to my research, and thus the construction of new theory was not a primary goal. Thematic analysis allowed for a reflexive, contextualised interrogation of underlying themes with a view to understanding the implications for trial design and governance, and thus was the technique that best aligned with the overall aims of my study.

Qualitative thematic analysis can be undertaken either inductively or deductively. In a similar way to grounded theory, an inductive thematic analysis begins with a very broad research topic, with the final research questions and themes suggested empirically from the data, whereas a more deductive approach would have at least some themes suggested before analysis, and a fully deductive approach would have pre-specified research questions, themes and code frames (Rivas 2018). My approach was largely inductive, in that the key themes and the final research questions emerged from the data, because my primary goal was to do justice to the perspectives and experiences of practitioners within the field, and as such it would not have been appropriate to impose my own theoretical framework from the outset. I did, however, approach the data with some preconceptions, influenced by the conceptual framework I set out in the previous chapter and my background reading on the topic of regenerative medicine and cell therapy trials. I thus used a number of 'sensitising concepts' to direct my analysis of the data. Sensitising concepts are used in qualitative research to direct the analyst's attention to particular areas of interest, without the more structured analytical framework imposed by the use of definitive concepts - in other words "whereas definitive concepts provide prescriptions of what to see, sensitising concepts merely suggest directions along which to look" (Blummer, 1999 quoted in Clarke and Braun, 2013, p.118). The sensitising concepts I used included Jasanoff's (2004) ordering instruments of co-production (making institutions, making identities, making representations and making discourses) and Keating and Cambrosio's (2007, 2012)

style of practice concept (the ways in which trials shape practice, and practice shapes trials).[3]

In line with this broadly inductive approach I adopted an open-coding process (Rivas 2018), initially coding a small amount of data using the sensitising concepts to direct my attention, but also identifying other issues and concerns that emerged. I then began to construct broader categories relating to these open codes, and then the overarching themes that structure the analysis in the empirical chapters of the thesis. For instance, the first stage of open coding might identify specific issues raised by interviewees or observations I noted in my field notes, such as "change in scientific perspective of MSCs", "problems scheduling trial participants for theatre", and "no QP available to sign of cells". These open codes then suggested broader categories, such as "basic science moves on quickly" and "practical issues delay trials", which then related to an overarching theme of "trial temporality". In line with the constant comparative method (Silverman, 2011, p.378), once I had started to develop categories from the open codes I interrogated them against further data, revisiting and refining the themes as my analysis progressed. To facilitate this I adopted an iterative, or zig-zag (Rivas 2018, p.433), approach to data gathering and coding, in that I began developing thematic codes before I had completed data collection. These preliminary themes then informed subsequent data collection, which then resulted in further refinements to the thematic coding and so on.

Throughout my analysis I attempted to treat the accounts of different participants (such as scientists, clinicians and trial professionals) in a symmetrical way, in that I didn't privilege one perspective over another but rather looked to understand how that perspective had developed and what impact it had. For instance, a number of clinicians described the funding situation for excess treatment costs in trials in a way that contradicted what I heard from other sources that could be considered more 'expert' in this area (such as trials professionals, representatives of commissioning groups and the NICE guidelines). However, I did not take this to

[3] The other main theme I discuss in the thesis is that of uncertainty, but this emerged from the data rather than being a sensitising concept from the start.

mean that the expert sources were 'right' and the clinicians were 'wrong', but rather I wanted to explore how they both came to have these different understandings of the situation, what use it might serve them to put forward this particular viewpoint, and how it affected their actions. I also aimed for methodological symmetry, in that I looked to explain all the perspectives I heard in the same way, regardless of how 'rational' or 'right' they appeared to be. For instance, one interviewee told me that a previous trial in their clinical area had a particular outcome, and I knew from having read the published results that this was indeed what was reported. Given my epistemological position, I did not consider it irrelevant that his account matched the published data and was therefore more likely to be 'true' in some sense. However, I did not take this to be a sufficient explanation for his perspective, and I thus looked to understand why he might have this understanding of the trial data and have expressed it in the context of the point he was making in the interview at that time, just as I would have done if the published data had contradicted his account.

Methodological symmetry was particularly relevant when comparing data from the interviews and observations with documentary sources such as peer-reviewed articles and policy documentation. McDonald (2008) suggests that qualitative analysis of documents should aim to establish not only facts but meaning, and as such can be undertaken at two levels - firstly examining the surface or literal meaning, and secondly a deeper meaning arrived at by some form of interpretive analysis. Thus I do not treat such documents as purely statements of fact, although I do use them as such in certain circumstances, for instance when constructing the dataset, characterising the policy and regulatory framework in Chapter 3, and reviewing the scientific literature on MSCs in Chapter 6. However, I also examine these documents in terms of the particular perspectives or representations of the field that they put forward, which are analysed in a similar way to other perspectives arising in different forms of data. In this way, I attempt to overcome one of the important tensions between approaches such as critical realism and contextualism and others that favour a more constructivist stance, which is that approaches that retain an interest in a singular truth risk marginalising experiential representations in favour of more 'objective' or 'factual' accounts (Parr, 2014).

Another important consideration for mixed methods research involves how the methods will be integrated. Onwuegbuzie and Johnson (2006) suggest that there are two ways to approach this integration: a dualist approach, which would involve having a purely qualitative part of the study and a purely qualitative part, or a continuum approach where a moderate approach is taken to both and they are considered alongside each other. My study involved both two types of data (qualitative and quantitative) and two types of analysis (descriptive statistics and qualitative thematic analysis). To some extent I took a dualist approach to their integration, in that I analysed qualitative and quantitative data separately, however most aspects of my approach were integrative, in line with the continuum position I took to the overall study (as explained in the previous chapter). Firstly, all the qualitative data analysis was undertaken in an integrated way, using thematic analysis. Secondly, I approached the quantitative analysis in a broadly inductive way that aligned to the qualitative thematic analysis, which meant that I did not pre-specify all of the analytical categories or undertake any formal hypothesis testing, but rather used descriptive statistics to identify and describe trends in the data. Thirdly, my focus throughout was on identifying and interrogating themes across the various types of data and analytical frameworks, using a process described by Alexander and colleagues (2008) as "following a thread". This involves emerging findings in one set of data being identified as having resonance in another, leading to a thematic thread that is then explored in other data, eventually resulting a data 'repertoire' which can then be interrogated further to generate an integrated account concerning that theme which is then linked back to the wider research question. For instance, in Chapter 5 I discuss a number of themes that first emerged in the case study and are then examined in the context of the interview data, and the theme of heterogeneity which I introduce in Chapter 3 first emerged in the quantitative analysis of the dataset and is then further explored through the interviews. To facilitate this integration I present the various data and analyses alongside each-other, for instance Chapter 3 presents descriptive statistics from the dataset intertwined with qualitative analysis, and Chapter 5 presents key themes emerging from the case study and then compares them to the interview data.

When deciding how to integrate various forms of data I also needed to make a decision about how they related to each other in an epistemological sense. I discuss the specific epistemological status of each strand of my research in more detail in the following section of this chapter, but before this it is helpful to briefly discuss their epistemological status relative to each other. Given that my aim was to explore the relationship between knowledge and reality I was not entirely unconcerned with understanding what that reality might look like, however I did not privilege one type of data or perspective as being better able to represent that reality. Rather, I treated them as providing various interpretations of the field, and it is in the interactions between these various interpretations that we can understand how science and social order are co-produced. The dataset thus does not present a more or less valid perspective than the interviews or the case study, but rather they all attend to different issues, and in different ways. The dataset presents a relatively formal, codified representation of the field that is recognisable to those within it, the interviews provide a more interpretive, nuanced and considered understanding of trialists' perspectives but still from a relatively macro viewpoint, and the case study affords a much richer, situated and in-depth picture of the work of trials at a micro-level. By integrating these distinct but complementary strands, I aim to present an account of cell therapy trials which is factually informative, empirically rich and highlights the diversity of perspectives and experiences I encountered during my fieldwork - all of which represent valid understandings of the field.

2.2 Methods

I summarised above the variety of methods I used to generate data, which included semi-structured interviews, observation and documentary/secondary data analysis. These different methods contributed to three overall strands of the research design:

1. Construction of a dataset of all cell therapy trials currently taking place in the UK, using data from a range of primary and secondary sources;
2. Semi-structured interviews with individuals involved in these trials;
3. A longitudinal, observational case study of one specific trial.

These three primary strands of research were supplemented with less structured forms of observation and documentary analysis. I attended a variety of relevant events, either as an attendee or a presenter, including a Medical Research Council training course on cell therapy trials, an Arthritis Research UK Tissue Engineering Conference, an MHRA patient consultative forum and the final conference of the REGenableMED collaborative project (to which my studentship was linked). I also interrogated a range of documentation, including policy reports, published articles, working papers, presentation slides, trial protocols and media coverage, some of which were publicly available and others that were provided by interviewees or academic colleagues. This combination of methods allowed me to develop a comprehensive understanding of the field, whilst also providing depth and richness of data. In the following section of this chapter I will discuss the rationale for the three main strands of data collection, detail how they were undertaken and explain how each was analysed and contributed to the empirical chapters of the thesis.

2.2.1 UK trials dataset

The need for a quantitative analysis of cell therapy trials began to become apparent to me fairly early in my research, because when I started trying to understand the characteristics of the field in order to plan my fieldwork I realised that it was often misrepresented or its complexities glossed over in much of the literature I was reading. For instance, although there is a lot of discussion about trialling and trials in policy literature and amongst the regenerative medicine community, when I started trying to identify actual trials I found very few. There were also many different and overlapping representations of what constituted regenerative medicine or cell therapy trials, which could be taken to mean any advanced therapy medicinal product (ATMP), any cell therapy (including for instance established treatments such as hematopoietic stem cell transplantation), specifically stem cell or embryonic stem cell therapies, specifically tissue engineered products and so on. STS research points towards the complexity of the field and the 'constellations' of different perspectives within it (see for instance Webster, 2013), but does not provide a specific depiction of the field of cell therapy trials that could be used to shape my own study, or be used to interrogate the 'conventional wisdom' about trials or inform a conceptual

analysis of trialling in relation to co-production and styles of practice. This suggested the need for a quantitative analysis of the UK cell therapy trials in the UK, in other words producing what Silverman (2011, p.11) describes as "a set of cumulative assumptions based on the critical sifting of data".

To conduct this analysis I constructed a dataset detailing the number and characteristics of cell therapy trials taking place in the UK at the time, using data from a range of primary and secondary sources, including trial registries, media reports, trial websites, and data from my interviews and observations. This dataset was useful in its own right as it provides the basis for the quantitative mapping of the trials landscape presented in Chapter 3. It also shaped the rest of the study by providing a sample frame for the qualitative interviews, helping me locate my case study site within the broader context of the field, and more generally creating a framework for defining what was in and out of scope, which as I discussed in Chapter 1 can be a particular challenge for interdisciplinary research. Taking a quantitative approach to this aspect of the research thus allowed me to address particular concerns that would not have been possible using a purely qualitative paradigm. However, critics of quantitative research argue that its reductionist approach results in the oversimplification of complex situations (Spicer, 2018, p.307), and that it relies on the use of an ad-hoc, subjective set of procedures to define, count and analyse its variables whilst making claims to objectivity (Silverman, 2011, p.13). With this in mind I set out here in some detail how I came to develop the procedures for constructing and analysing the data, highlighting the complexity and provisionality involved, and then consider at the end of this section how this affects my positioning of the dataset and its epistemological status.

The term 'cell therapy' can be defined in various ways, and thus a number of decisions needed to be made about which trials would be included in the dataset. Firstly, the dataset could be limited to trials of 'stem' cells, which was the approach taken by some similar studies, such as Li et al. (2014) and Foley and Whitaker (2012). Alternatively, following other researchers such as Heathman et al. (2015) and Culme-Seymour et al. (2012), the scope could be broadened to include all therapies that use cells as a therapeutic agent (i.e. including somatic cells as well as stem cells). I decided

on the latter approach, for two main reasons. Firstly, there is still disagreement in the scientific community about what actually counts as a stem cell - for instance, as I discuss in Chapter 6, there is much debate as to whether MSCs should be considered 'stem' or 'stromal' cells. Limiting my research to stem cells would thus lead to uncertainty about the classification (and therefore inclusion or exclusion) of some trials, as would the fact that for a number of trials there was not enough information available to make a definitive judgement about the exact type of cells used. Secondly, a significant proportion of current UK trials are testing somatic cell therapies. Given that these trials would likely be relevant to the research questions, excluding them would have unnecessarily limited the data available for my analysis.

Another important decision related to the therapy's mode of action. Not all cell therapies have a regenerative mode of action, and some researchers question whether these treatments can really be considered regenerative medicine (see for instance Weissman, 2012; Kemp, 2016). However, excluding non-regenerative treatments would have been problematic for a number of reasons. Firstly, it is not necessarily possible to differentiate between treatments that have a regenerative effect and those that don't, because the underlying mechanisms of most cell therapies are still poorly understood. Indeed, for more than one trial it appeared that the original aims were regenerative but the scientific literature as it stands now suggests that the treatment probably has a different mode of action. Secondly, there was often very little information available about the mode of action of the treatment, meaning it would have been difficult to accurately categorise many trials. Thirdly, much of the academic and policy literature, whilst using the term 'regenerative medicine', actually encompasses all cell therapies, including those with a non-regenerative mode of action (see for instance House of Lords, 2013).

Taken together, these factors suggested that it was neither practical nor necessary to exclude non-regenerative cell therapies entirely, and instead I included the mode of action as a variable in my analysis. I thus defined the scope of my study as encompassing all trials of cell therapies currently taking place in the UK. Following Li et al. (2014) I excluded observational studies, trials where the cell therapy was not the subject of investigation (e.g. those investigating supportive measures), and trials

of established therapies for established indications (i.e. hematopoietic stem cells for leukaemia). Using a list of trials produced by the Cell and Gene Therapy Catapult (CGTC, 2015) as a starting point, I validated each trial as fitting my criteria, based on the scope defined above. I then verified that the trial was currently underway by checking that its registry entry indicated the study was either in set-up, currently recruiting or in follow-up. I checked the completeness of the dataset by interrogating other sources to identify any trials that might have been missed, including the NIHR portfolio database, industry publications, media reports and word of mouth. Once the full set of included trials was defined, I collected information about a variety of aspects of each trial, including the type of cells, the manufacturing process, the trial design, the sponsor and the funder.

This process resulted in a set of data about the characteristics of UK cell therapy trial that is as comprehensive and valid as possible, however there were a number of factors that must be considered when considering how accurately it reflects the reality of the field. Firstly, although I cross-checked as much as possible to maximise the accuracy of the final dataset, much of the data was sourced from secondary sources (such as online trial registries) that may not be complete, accurate or up to date. Furthermore, the data available was often incomplete or vague, and there were inconsistencies between data sources, so there was an element of judgement and assumption involved in the data collection. As this was only conducted by one individual there was no opportunity to check for inter-rater reliability (Seale and Tonkiss, 2018), although I have attempted throughout to be as transparent as possible about the framework I used for making these decisions. Thirdly, the analysis was of necessity conducted at the beginning of my research, and thus is slightly out of date. For instance, the CGTC produced an updated list of trials in 2016, which indicated a number of changes from the previous year. The overall picture and trends, however, are unlikely to have changed significantly, and thus the dataset still presents a useful basis for this study.

The dataset is mainly used to address my first research question by characterising the field of cell therapy trials in the UK, and as such the aims of the analysis were to identify and describe broad themes rather than test specific

hypotheses. As the data represented the entire population of cell therapy trials (as I defined it) I did not use inferential statistics, which would be used to explore the relationship between representative sample and the population it is intended to represent, but rather I used descriptive statistics, which are a useful way to describe and summarise a given set of data (Proctor, 2008). I thus did not perform tests of statistical significance or test specific hypotheses, which also aligned with my overall analytical stance, which favoured an inductive rather than deductive approach to the analysis where possible. I used frequency distributions and cross-tabulations to describe the data, using analytical categories that were informed by my background reading and comparisons with other studies, for instance the type of cells (autologous or allogeneic), and also by the sensitising concepts I described earlier (for instance the style of practice concept suggested an examination of clinical area). In line with the inductive analytical framework, and to enable me to 'follow the thread' as I described earlier in this chapter, I also created analytical categories based on emerging themes - for instance uncertainty about the mode of action of cells began to emerge as an important concept during my fieldwork, so I included this as one of the analytical categories for the dataset. This approach created a detailed quantitative analysis of the various contexts and characteristics of trials, and enabled comparisons with the global picture reported in other academic studies. It also provided an opportunity to interrogate 'conventional wisdom' about cell therapy trials – represented, for instance, by media accounts of the field and in the regulatory and policy framework - and to assess how this wisdom compares with current trials activity.

In one sense this analysis of the dataset can be understood as representing an account of 'the field' that claims to represent reality, and against which other claims can be judged. However, the uncertainties and subjectivities involved in constructing the dataset that I discussed earlier suggest that it is more appropriately considered in a more constructivist sense - as a useful tool for problematising the representations of the field that are visible in the media, policy and regulation, but one that in itself must also be considered provisional. Furthermore, the sources of information I used to construct the dataset are themselves only representations, and

the differences between them highlight the multiplicity of these perspectives. Rather than representing one singular reality of cell therapy trials, then, I consider the dataset as providing one particular perspective on the field, and I focus on interrogating how this aligns with or challenges other perspectives (such as those presented in other academic literature, assumed in regulation or put forwards by various interviewees). Because of this I attempt to draw out in my description and analysis of the dataset the provisionality of its perspective - for instance earlier in this chapter I documented the various other ways the field has been constructed in academic literature, and in Chapter 3 I discuss how these different approaches align with or conflict with my own representation. Chapter 3 also considers how different constructions or interpretations of the dataset would lead to different depictions of the field, for instance the effect of categorising MSCs differently, or excluding non-regenerative treatments. Thus I do not suggest that this dataset is the only way to understand the reality of cell therapy trials, rather I present it as a useful counterpoint to other representations of the field, and as a starting point for unpicking the synergies and tensions between these various representations.

2.2.1 Semi-structured interviews

One of the main objectives of my study, underpinning all the research questions to some extent, was to unpick the range of experiences, interactions, representations and challenges that emerge from cell therapy trials. There issues could in principle have been explored to some extent in a survey or standardised interviews, but qualitative interviews have a number of features that made them more appropriate for both the aims of my research and my epistemological position and analytical approach. Qualitative interviews promote an 'exploratory' analysis of a phenomenon rather than the testing of hypotheses (Jones, 1985, in Seale, 2004), and are thus better suited to an inductive analytical approach. Open ended and flexible questions are also more likely to get a considered response than closed questions, thus providing better access to interviewees views, interpretations of events, understandings, experiences and opinions (Byrne 2018) - the lived experience and meaning that I was interested in understanding. Open interviews can also achieve a level of depth and complexity that is not possible in other, particularly survey-based,

approaches (Byrne 2018), which was important for my study both because of the complexity of the subject matter and the multiplicity of perspectives that I identified in my background reading. Perhaps one of the most important benefits of the qualitative interviewing for my study is that the interviewing process prompted interviewees to reflect on the meaning of their own experiences. In the words of Charmaz and Bryant, qualitative interviews can create "a special social space where interview participants can reflect on the past and link it to the present and future in new ways" (Charmaz and Bryant, 2011, quoted in Silverman, 2011, p.204). Qualitative interviewing thus allowed me to understand how trialists understood and made sense of their own experiences of trials, and to reflect on how these experiences fit into the broader contexts and interactions involved in cell therapy translation.

Qualitative interviews are ideally conducted face to face, as this allows for a greater rapport to be developed and the interviewer to monitor non-verbal cues and body language as well as what the interviewee says (Byrne 2018). For these reasons I conducted most of my interviews face to face, although three were conducted by phone for practical reasons (one person was based in the US and two were unable to commit to an exact time for a face to face interview but were more flexible by phone). I obtained approval from the University of York Economics, Law, Management, Politics and Sociology (ELMPS) ethics committee. As the interviews did not involve patients, NHS Research Ethics Committee approval was not required, although for those interviews taking place on NHS premises local research governance approval was potentially needed. However, this only applied to two interviews as all the others were conducted either on university premises, in hotel lobbies/cafes or over the phone. For both the interviews conducted on NHS premises I contacted the local R&D department, who confirmed that they would not need to issue formal approval for this kind of interview.

Unlike structured, standardised interviews intended to elicit largely quantitative data, qualitative interviews tend to be relatively unstructured and flow more like a conversation (Fielding 2008). Byrne (2018) suggests that the key aim of qualitative interviewing should be to encourage an interviewee to talk, but crucially to focus the conversation of topics that you are interested in researching, and the

approach to this can range from the extremely inductive single-question induced narrative approach, whereby interviewees are asked a single question and asked to talk about it with no further questions or prompts, to a structured topic guide that lists a series of questions and follow up prompts in a relatively deductive framework. My approach fell somewhere in-between the two, in that I developed a broad discussion guide (detailed in Appendix 1), but I did not adhere rigidly to this during the interviews but rather let the interviewee shape the conversation, only coming back to the discussion guide if they strayed significantly from the areas I wished to understand. I also adapted the discussion guide slightly for each interview, based both on the specific circumstances of the particular interviewee and the themes that were emerging during my fieldwork. In line with my interest in understanding the day-to-day work of trials and their role in co-production, I focussed the discussion on interviewees experiences, including their role in designing and undertaking the trial and their understanding of its value to their wider objectives, as well as the challenges they had experienced, the effect of these challenges and how/if they had overcome them.

Because of the time involved in undertaking qualitative interviews it is usually not possible to achieve large samples (particularly when the interviewers are only conducted by one researcher), and as qualitative research does not aim for statistical generalisability random or probability samples are not necessary (Byrne 2018). However it is still important to consider who should be interviewed in order to gain a good understanding of the field, and Byrne suggests that the first stage to this must be considering the wider population from which you will select your interviewees. The dataset I constructed helped to define the scope of this wider population by identifying the specific trials that were taking place, and further to this (in line with my situating of trials as a social process) I decided to focus specifically on individuals who were actually participating in the work of the trial, rather than for instance regulators, policy-makers or other stakeholders who might have a more external or arms-length involvement. I then needed to decide how to construct a sample of this population, which could be representative, meticulous, or a relevant range (Mason 1996, described in Byrne, 2018). Representative samples involve ensuring the sample

is representative of the total empirical population, which requires knowledge of the characteristics of that population and statistical tests to ascertain how representative the sample is. This is not a common practice for qualitative research, and was neither possible nor necessary for my study, which did not aim to draw any statistical generalisations from the data. Meticulous samples aim to provide a close-up detailed view of a particular experience, and as such could be relevant to my study - indeed this is essentially how the sampling strategy for the case study can be understood. However, choosing this approach for the interviews would have limited my ability to explore the range of experiences of participation in trials, which was the primary focus of this strand of the research. I thus decided to select a relevant range of individuals involved in trials, in that rather than being statistically representative I aimed for the sample to be a good representation of the field, meaning that I ensured that it covered the full range of different types of trials and the variety of individuals involved in them.

I conducted 17 interviews in total (14 face to face and three by telephone), with durations ranging from 45 minutes to two hours. The total number of interviews was to some extent dictated by practicality (i.e. the amount of time available for this part of my research), and also by the availability of interviewees, because I contacted every individual I identified as being involved in trials and interviewed all those who were willing to participate. I also considered whether data saturation had been reached (Silverman, 2011, p.73), which was somewhat difficult to judge because the heterogeneity of the sample, and of cell therapy trials themselves (discussed in Chapter 3), meant that every interview generated new information. However, by the final interview I felt that all the new information generated was factual rather than thematic – i.e. it related to the specific characteristics of the trial in question, rather than the broader codes, categories and themes I was developing.

In the interests of anonymity (of which more below) I will not detail the exact characteristics of each interviewee, but rather I summarise their main role in trials (Table 2.1). There was in fact a lot of fluidity in this - for instance a commercial contact might also be a cell manufacturer, or a clinician might be involved in commercial trials. In total, five interviewees had some involvement in commercial trials and 14 were

also involved in non-commercial trials, which is broadly aligned with the overall UK landscape detailed in Chapter 3.

Table 2.1: Interviewees' main role in trials

Clinicians / clinician-scientists	8
Scientists / cell manufacturers	4
Trial professionals	2
Commercial contact	2
Advisor / consultant	1

The sample covered a wide range of cell types, including MSCs, HSCs and neural cells, and there was also a combination of both autologous and allogeneic therapies and of both ATMPs and non-ATMPs. In terms of mode of action, the interviews covered immunotherapies, regenerative therapies and other therapeutic uses of cells, and the clinical areas included oncology, neurology, auto-immune diseases, musculoskeletal, diabetes, MS, cardio-vascular and stroke. The sample also covers all stages of the trial process, ranging from pre-clinical work to in set-up, open and completed trials. Although this sample largely achieved my aim of being a good representation of the field, it does have two limitations which should be noted. Firstly, it is largely made up of individuals involved in trials that had either been successfully set up or were fairly well advanced in planning. There is thus an element of selection bias in the sample, because individuals who might have tried and failed to set up a trial are underrepresented. This is to some extent inevitable, as it would have been very difficult to identify such individuals, however I attempted to account for it as much as possible by speaking to people from the CGTC pre-clinical database as well as the clinical one, and I also interviewed an individual from an innovation accelerator agency, who had experience of supporting cell therapy developers early in the trials process. Secondly, as I noted above, the sample is extremely heterogeneous, being made up of a range of professions, types of trials, clinical areas etc. This heterogeneity presented challenges in terms of data analysis, for instance the difficulty in assessing data saturation which I mentioned above. However, this heterogeneity was

unavoidable, and is in fact one of the key findings of my study; the field of cell therapy trials is itself extremely heterogeneous and fragmented, and thus a more homogenous sample would in fact have impeded, rather than improved, my understanding of the field.

To construct my sample I identified key contacts for each trial using sources such as the CGTC database, online trial registries, press releases, trial websites and word of mouth. I then emailed these contacts inviting them to participate in an interview, with a follow up email sent two weeks later to everyone who had not responded. All those who indicated they would be happy to participate were then sent a copy of the participant information sheet and consent form to review (see Appendix 2), and a time and location were arranged to conduct the interview. At the beginning of each face-to-face interview I gave the participant a paper copy of the information sheet, checked that they had read and understood it, and asked them to sign the consent form and confirm they were happy for the interview to be recorded. For interviews conducted by telephone I obtained email consent prior to the interview, or verbal consent at the start of the call, having confirmed that they had read the information sheet and answered any questions they had.

In line with the recommendation of the ethics committee and the commitment made to my interviewees, all the data from the interviews is anonymised in the analysis. This proved to be relatively challenging, because the very small number of trials taking place means that providing any detail about the interviewee's role, or the specific trial they work on, would make it easy for someone involved in the field to identify them. Indeed, in such a small field, and given the very public profile of some of my interviewees, there is a danger of some of them being recognised from particular phrases they use or points they make, which may have been published or presented elsewhere. Maintaining the anonymity of participants in such circumstances can be problematic (Saunders et al., 2015), and requires a balance between providing information to contextualise the findings and concealing it in order to protect identities. Saunders et al. make some useful suggestions for mitigating these issues, and inspired by these I have adopted a specific approach to the reporting of my interview data. To maximise anonymity, I refer to each

interviewee by a number only (e.g. Interviewee 1, Interviewee 11), rather than describing their role in more detail, as is often seen in the analysis of interview data. I also do not list the characteristics of each of the interviewees at an individual level, for instance their role in the trial or the type of cell used. To provide as much context as possible, however, I have provided this information in summary form (see above), to demonstrate the range covered by the sample. I also give specific contextual information for individual quotes where it is necessary in order to fully understand the point being made. I keep this information deliberately vague, however, to limit the possibility of 'piecing together' a profile of any one interviewee from contextual information given in different parts of the thesis.

All the interviews were recorded with a digital voice recorded, and I transcribed the recordings myself to familiarize myself with the data (Fielding, 2008, p.258) before analyzing the transcripts using the thematic content analysis approach that I described earlier this chapter. Rivas (2018) advises qualitative analysts to look beyond the surface of interview data and ask interpretative questions of it, such as 'what is happening here" and "from who's point of view?" The questions I paid particular attention to included what exactly was being described, why is was being described like that, what meaning the interviewee was giving to it, and how did this relate to other things they described in the interview, as well as things other interviewees had said or that I had observed. I also considered what interviewees might not be telling me, because as Charmaz points out, "silences have meaning too" (Charmaz, 2002, quoted in Byrne, 2018). Charmaz suggests that silences might arise from things the interviewee either doesn't know, has forgotten, doesn't understand or doesn't think is relevant, but they can also be deliberate - a withholding of information that may be by choice, but could also be imposed. This became particularly salient to me when one interviewee asked me to turn off the tape during an interview and told me something that he felt could lead to him being sued if it ever came to light, because he had signed a confidentiality agreement which prohibited him from disclosing it to anyone. At his request I do not present this specific issue in my analysis because the circumstances were so specific it would be impossible to ensure he wouldn't be identified. The incident did however point my attention

towards the potential effect of confidentiality agreements on the willingness and ability of my interviewees to speak freely, and also more broadly to the fact that in such an ethically contentious field there could be many reasons an interviewee might choose to withhold, or 'sanitize', certain information or views.

This issue points towards the importance of considering the epistemological status of the interview data in my qualitative analysis. A positivist interpretation of interview data would suggest it provides direct access to facts (Silverman 2011), and indeed this is implied in my use of data from the interviews to construct the quantitative dataset. In the qualitative analysis, however, I was interested in uncovering the range of experiences and perspectives my interviewees described, rather than accessing one singular 'truth' about these experiences. As such I treat the interview more as a topic than a resource (Silverman, 2011, Rivas, 2018) – i.e. I am more interested in how and why information is being communicated and the accounts being told, rather than the specific factual information it contains. As Byrne (2018) points out, it is never really possible to get inside an interviewee's head, and thus what an interview produces is always a particular representation or account of an individual's views or experiences. Thus I do not treat the interviews as necessarily completely authentic accounts, but rather as a co-constructed (Silverman, 2011, p.181) between myself and the interviewee, influenced by a myriad of known and unknown factors, such as the constraints of confidentiality or the fact that the interview may have been the first time the interviewee reflected on some of the issues being discussed. This gives the interview data a particular epistemological status in relation to both the dataset and the case study - it is more interpretative than the quantitative analysis and thus helps to provide context and meaning to the abstracted nature of the descriptive statistics, but it reflects a series of considered, co-constructed perspectives of the trials process rather than providing direct access to trialists' experiences, which is one of the purposes of the case study that I will now go on to discuss.

2.2.3 Observational study

Although the interviews generated rich and insightful data about the experiences and perspectives of cell therapy trialists, there were clearly limitations on the insight they

could provide into the day-day-day work of trialing. Interviews are by their nature relatively short, imposing a practical limit to the amount of information that can be covered; the impact of this was particularly noticeable in this study because the complexity of the issues being discussed meant a significant proportion of the interview was often spent covering only a small portion of the discussion guide. Interviews also take place at a specific point in time, and given that many of the events I was asking about took place a long time ago interviewees' recall may not have been completely accurate - indeed, some may not have understood the issues completely even at the time. Furthermore, as I noted above, the data is also clearly limited to what the interviewees were prepared to share in a relatively formal context, and shaped by their own specific preconceptions and concerns, and the interview process itself. Thus, although most of my interviewees were remarkably candid and forthcoming, there was no doubt much pertinent information that they had either forgotten, never known, or chose to exclude during our discussions.

If interviews can be understood as limited to understanding what people say they think or feel in the specific interview context, then ethnography provides an alternative viewpoint by turning the focus to examining what people actually do (Silverman, 2011, p.118), underpinned by a belief that knowledge of social phenomena can only be gained by direct experience (Hammersley, 1991, in Seale, 2004). Ethnographic research typically (although not always) involves some form of direct observational fieldwork, which can help to overcome many of the limitations of interviewing - for instance by making visible the matters interviewees are unable or unwilling to talk about, providing the researcher with direct access to phenomena that interviewees might represent through a 'distorted lens', and allowing for analysis of process and context which can become hidden when an experience is described and summarised retrospectively (Becker and Geer, 1969, in Seale, 2004). Some of the most important insights generated by STS have emerged from its rich tradition of laboratory ethnographies, which have highlighted how scientific knowledge emerges from the procedures, negotiations and interactions of scientific work itself (Sismondo, 2009, p.108). In order to really understand the doing of cell therapy trials,

then, it was necessary to not only discuss the process retrospectively in interviews, but also to observe the work of the trial occurring first hand, in real time.

The original proposal for my studentship planned for two placements at sites undertaking cell therapy trials, with the intention that these would provide opportunities to undertake ethnographic research. Early on, however, it became apparent that this would be practically difficult for a number of reasons. Firstly, when I started to look for trials taking place in the UK I found that although there was a significant amount of preclinical work taking place, there were in fact very few actual clinical trials, and of these many were either in follow up or in set up, meaning there was no actual 'trialing' work happening at the time. Secondly, most of these trials were very small and would not have represented a large proportion of the work being undertaken at the site, so I could potentially have spent a long time observing without ever seeing any of the work of the trial. I was also concerned that unlike laboratory work, which coalesces around a particular place and activity, the work of cell therapy trialing is relatively dispersed, with activities taking place in various locations (such as clinics, cell labs and operating theatres). At a busy trialing site, with personnel whose only work activity involved trialing, it might be possible to access these activities through shadowing or observing in a particular location, but for a cell therapy trial that only aimed to recruit perhaps ten patients over a two-year period, much of the work I could observe like this might not relate to the trial at all. Thirdly, most trials were located a long distance from the University of York, so the amount of time I would actually be able to spend on site would be limited by travelling time and expenses. Furthermore, as trials take a significant amount of time to set up and run, any placement would have to cover a relatively long period of time in order to really see the work of the trial, which would not be practical if the site was not within a manageable travelling distance.

These considerations led me to reconsider the plan to undertake two separate and relatively time-limited placements, and instead focus on finding one site where I could access as much of the day-day-day work of a trial as possible and could observe over a longer period of time. One of the sites I identified appeared to be promising in this regard: it was running a relatively large trial which was embedded within the

work of the whole department, it was a short enough distance away that I could travel there for the day, and their links with my biology supervisor's research group meant the team were enthusiastic about having me become involved in their work. When I first visited the site to discuss my research they described the management of the trial to me and it became clear that they held regular, scheduled team meetings, which provided an ideal focus for my observational work. By planning a series of visits that coincided with these meetings I was able to ensure that at every visit I would be able to observe work specifically related to the trial, and this allowed me to stagger a series of productive visits over an 18-month period. During these visits I conducted observational research, the majority of which involved attending the fortnightly trial team meeting but also included sitting in the trial manager's office whilst she was preparing for the meeting, having discussions with the research nurse and updating the research governance manager. I also observed work being undertaken in the cell processing and scientific research labs, attended a large conference/meeting the team convened with other centres involved in similar cell treatments, and participated in other events taking place in the site's wider research network.

The case study fieldwork was approved by the University of York ELMPS ethics committee, and as no patients were involved it did not need NHS REC approval. The research took place on NHS premises, so local research governance approval was required. On advice from the site R&D department I applied for an NHS Research Passport, which allows academic researchers to undertake fieldwork on NHS sites. Once this was issued I was given approval to access the site to conduct interviews and observational research. I gave a short presentation about the study at the first team meeting I attended and answered any questions that were raised. All research participants were then given an information sheet about the study and a consent form to sign (Appendix 3). The information sheet indicated that the site itself would not be anonymised, because in this instance I felt that complete anonymity could not be guaranteed for two reasons. Firstly, as highlighted by Saunders et al. (2015), insider status can be problematic for anonymization, and in this instance my contact with the site came through one of my supervisors, and it is common knowledge in the field that he is involved with the site. Secondly, as with the interviews, the small size of the

field means that any description of the site (including the size of the trial, type of cells or clinical area) would immediately identify it. It was possible to overcome this issue for the interview data using the strategies I described earlier, but much of the richness of the observational data would be lost if I had to expunge all contextual information. For all of these reasons, I made the participants aware that the site would most likely not remain completely anonymous, although on the advice of the ethics committee I have still taken every possible step to maintain anonymity where possible. I therefore will not identify the specific trial or the site where it took place, and will refer to it instead by the pseudonym ENABLE.

The ENABLE site includes a clinical team (who are involved in surgery and follow-up care), a cell manufacturing facility and a linked scientific research unit. Although for the purposes of anonymity I will not detail the specifics of the treatment or clinical area, these were both relatively typical for the field.[4] Table 2.2 (overleaf) details the key individuals involved in the trial; I have used pseudonyms here rather than another form of anonymization (such as referring to them by their role) because I feel this best represents the more engaged and personal nature of the involvement I had with the team during my fieldwork, in contrast to the more arm's length nature of the interviews. I have chosen to make these pseudonyms gender-correct, because although this potentially makes it easier to identify individuals I felt that gender was relevant to the social dynamics of the team, and thus it was important to preserve the gendered nature of the data. I first made contact with the site through the head of the scientific research unit, Claire, and arranged to visit and discuss my study. At this visit we agreed that I could access the site for my fieldwork, and Claire introduced me to the Trial Manager, Amy, who helped me to set up the study, organise research governance approval and plan my visits and interviews. I then visited the site approximately once a month over an 18-month period to observe the team's activities, visiting 16 times in total for between three and six hours per visit.

[4] Although, as I will show in Chapter 3, the concept of a 'typical' cell therapy trial is in fact highly problematic, and thus no trial can really be considered typical of the field.

Table 2.2: Main individuals involved in the ENABLE trial

Mr. Hamilton*	Surgeon / Chief Investigator
Mr. Jones	Another surgeon involved in the trial
Amy*	Trial manager
John*	Statistician
Claire*	Head of scientific research unit
Mark*	Cell manufacturing lab manager
Harry	Radiologist
Kelly*	Scientific researcher
Geraldine	Scientific researcher
Rebecca	Research nurse

** Semi-structured interview conducted*

There are four broad observational roles for a researcher in the field: complete participant, participant as observer, observer as participant and complete observer (Walsh and Seale, 2018). To begin with my role could best be described as observer as participant, meaning my role was made public at the outset but I didn't actually participate in the work the team were undertaken. This positioning of the fieldworker's roles can provide access to a wider range of information, and even secrets, than would be possible through complete observational research, which would have had to be at entirely public-facing events (Junker, 1960, in Seale, 2004), but also introduces reporting constraints because of ethical responsibilities to the participants who chose to 'let me in' to their world. During the progress of my fieldwork I moved more towards the role of participant as observer, as I become involved to some extent in the work being undertaken at the site. For instance, the team tended to view me as an outside expert on trial design and were also aware that I was investigating a number of other cell therapy trials. Because of this they occasionally asked for my opinion on a particular methodological issue, or for information about how things were done at other sites. In another example, when the wider research network submitted a bid for the renewal of their funding, I

contributed a section on the purpose and benefits of my own research, which they positioned as an important collaboration that added value to the centre. I felt that being 'useful' in this way helped me to better understand the issues the team were facing, and it also made me feel more comfortable with the imposition that my fieldwork must have placed on an already busy department. I also think that it made the team more comfortable around me, and thus more forthcoming than they might otherwise have been, thus I felt that the role of participant as observer won me acceptance more as a 'good friend' than a 'snooping observer' (Junker, 1960, in Seale, 2004), which brought with it an implicit bargain that my work would be supportive rather than detrimental to their own.

One of the most important benefits of the ENABLE site was the fact that they held regular team meetings, providing a structured opportunity to observe the work being undertaken by the team. In contrast to the clinical or laboratory aspects of a cell therapy trial, the decision making, interpretation and negotiation that underpin the knowledge practices involved might be expected to be relatively 'invisible', taking place for instance in someone's head, or in work that they do on a computer. Garforth (2012) found that this issue of visibility is particularly problematic for office-based social science research, where "without the methodological convenience of the lab, knowledge practices were rarely on show but rather retreated into solitary spaces or coalesced fleetingly in meetings." Indeed, one of the drivers for early STS laboratory studies was the fact that so much of laboratory work is relatively 'visible' (Sismondo, 2009, p.106). Meetings, then, provide a rare and possibly unique opportunity to observe the knowledge practices at work in clinical trials, and are in themselves an important topic of study. Boden (1994) argues that meetings are "the very social action through which institutions produce and reproduce themselves". As such, the team meetings were a crucial opportunity to understand the ongoing challenges and decision making involved in undertaking the trial, and how the 'talk' of the meeting structured the 'organisation' of the trial. In particular, Boden highlights the fact that meetings are where the various different agendas and coalitions involved in an organisation come together, and indeed the ENABLE team meeting brought together the disparate parts of the trial, such as clinicians, statisticians and scientists. This

made it possible to observe the interactions between all of these areas in a way that would not have been possible had I only observed their individual activities.

As the team meetings were such an important part of my ENABLE fieldwork, and indeed of the trial itself, it is useful to consider their specific characteristics. Boden distinguishes between large formal meetings, which are primarily information-oriented, and smaller informal meetings, which are more decision-focused. The ENABLE meetings were largely informal, in that although they were scheduled for a particular time there was no formal agenda or minute-taking, no designated time limit (the meetings I attended ranged from 30 to 90 minutes long), no designated chairperson and no restricted or directed turn-taking. Although there was some information shared at the meetings (for instance Amy would normally provide updated recruitment figures and Mark would share information about upcoming/completed lab inspections), their purpose was primarily decision making. Most members of the team interacted fairly regularly outside of the meetings and shared trial-relevant information in various ways, so the meetings were an opportunity to discuss this information as a group and make decisions that were, in principal anyway, collaborative. Boden suggests that meetings are a 'contained' communication activity, in that they have a defined beginning, middle and end, with interruptions being discouraged. However, the ENABLE meetings in fact appeared to accommodate a considerable fluidity, making them more an integrated part of the working day rather than a defined, contained activity. For instance, attendees would often arrive late, leave early or leave and then return, all with the active approval of other participants, and individuals not involved in ENABLE would occasionally 'pop in' to discuss a different piece of work. The early stages of the meeting sometimes involved discussions of other work activities not directly linked to the trial, and discussions started in the meeting were often continued in various groupings after it officially ended, and occasionally moved to other locations such as the lab or the consultant's office.

Given the importance of meetings in structuring the work of an organisation, membership is an important consideration (Boden, 1994). Membership of the ENABLE meetings was determined by both invitation (there was an open invitation to

all individuals deemed to have an interest in the trial) and by the choice to attend. Peripheral members of the team, such as Harry, Geraldine and Mr. Jones, only attended very occasionally, and thus became largely outside observers rather than active participants in the structuring of the trial organisation. Although the number of attendees was occasionally low (on one occasion only Amy and Claire were there for the majority of the time), the majority of meetings were attended by most members of the core team. The most senior members of the team, who had many other calls on their time, were rarely absent, indicating the importance they placed on this activity in ordering their work. Boden suggests that meetings cannot start, and in some ways do not exist, unless there is a perceived critical mass present, and in the case of ENABLE this critical mass appeared to be a minimum of two - which could on occasions mean only one of the team members and me. Although discussions would start as soon as there were two people in the room to talk, this talk would be different depending on which team members were present, and in meetings where individuals arrived and departed at different times the discussion would shift, repeat, expand and contract depending on the various voices and concerns in the room. Of particular note was the ongoing absence of the Research Nurse, Rebecca, who was invited to the meetings but was rarely able to attend because they conflicted with outpatient clinics where she would be speaking to trial participants. In the context of the meetings being an active process of structuring the 'organisation' of the trial, her absence meant that despite being perhaps the most involved in undertaking the daily trial activities, she was the least involved in structuring these activities.

Although observing the team meetings provided an extremely rich source of data about the day-to-day activities of trials, observing the interactions and 'talk' in the meetings did not provide the full picture of the work being undertaken by the individuals involved. I therefore decided to supplement my observational fieldwork by conducting semi-structured interviews with key members of the team (indicated with an asterisk in Table 2.2). Although some ethnographers are critical of interviews, preferring to focus solely on naturally-occurring data, in some cases they might be the only way to collect important data (Walsh and Seale, 2018). My interviews

allowed me to flesh out my understanding of the activities undertaken by individuals involved in the trial, which was not always fully apparent in the meetings, and also to clarify points that I had not completely understood in the meetings. Because the trial was already open by the time I started my fieldwork, the interviews were also the only way to find out about the decisions and activities involved in setting it up, and to understand its perceived purpose and value.

The interviews lasted between 30 and 60 minutes and were all either arranged in advance of one of my regular visits or agreed during the team meetings. I did not use a generic discussion guide because each of the individuals in the team has a very different role on the trial. Instead, I prepared a number of specific questions for each interviewee, which ranged from clarifying specific aspects of their role or things I had noted from documents or observations, to more generic questions about their experience of the trial and what they perceived to be the key challenges. The interviews were recorded, and I followed the same process for transcribing and coding that I described earlier for the other interviews I conducted. In addition to these arranged interviews, I also conducted a number of more informal interviews and discussions. For instance, at each visit I had a brief discussion with Amy after the team meeting to clarify any points I hadn't understood, and I also often had more informal discussions with other members of the team whilst we were waiting for the meeting to start, or when I was being shown around parts of the site. These discussions were not recorded as they were often quite ad hoc, and it would have been intrusive to ask permission to turn on the recorder. I also wanted to preserve the more informal nature of the discussion, so that these accounts remained relatively unsolicited in comparison to the more prompted nature of the scheduled interviews (Walsh and Seale, 2018).

Although the pre-arranged interviews were recorded and transcribed, the rest of my ENABLE fieldwork (including informal interviews and observation) was documented using handwritten and typed field notes. Field notes should ideally be written as soon as possible so the activity is still fresh in the researcher's memory (Walsh and Seale, 2018), and to aid with this I made some limited written notes whilst observing to help me recall the main points and capture any particularly interesting

verbatim quotes. I avoided making detailed notes at this point in order to focus on listening to and watching the conversation, which often moved very quickly so if I lost the thread whilst writing notes it could take a long time to pick it up again. I also wished to avoid making the team feel that I was 'snooping' on them as much as possible, which might have altered their conversations. After leaving the site I would stop in a cafe for an hour and expand these handwritten notes, and then the next day I typed up my field notes in full, using my hand-written notes as a guide.

When analyzing observational data, Silverman emphasizes the importance of distinguishing between *emic* observations, which emerge from the researcher's conceptual framework, and *etic* observations, which arise from the conceptual framework of the site and its participants (Silverman, 2011, p.83). To aid with this I followed Lowland's advice on the different elements that should be captured in field notes, and how they should be distinguished (Lowland, 1971, in Seale, 2004). Firstly, my field notes included running descriptions of the activities I witnessed, which I kept concrete and descriptive, and I also noted the individual who expressed a particular view and how this was received by others. Secondly, my field notes included emerging analytical ideas, which I marked as such to distinguish them from observations - in my hand-written notes these were marked with my initials and boxed off from the other notes, and in the typed notes they were highlighted in yellow. Thirdly, my notes included personal impressions and feelings, where I recorded my own experiences and feeling about the setting as well as the things I observed, including any issues that I felt might raise ethical concerns. Finally, I made notes of further information that I wanted to investigate later, for instance clarification of a particular technical point, or information about the background to a particular discussion, and also any points that had relevance to the other strands of my research (for instance something that might relate to a future interview).

The process of writing these field notes was not only a means of recording information that I might otherwise have forgotten, it was also the first step in the analytical process. Following Walsh and Seale (2018) I kept my field notes very broad to start with, but as my fieldwork progressed I started to hone in on the particular themes and concepts identified in my analytical notes (and more widely in the other

strands of research I was undertaking), and these then started to shape my future note taking. I then analysed my field notes, along with trial-related documents I acquired during my fieldwork, using the same thematic analysis technique I described earlier in this chapter.[5] These findings underpin the analysis in all the empirical chapters, but are particularly drawn out in Chapter 5, which discusses themes relating to the challenges of cell therapy trials that emerged from case study and interrogates them in the context of the interview data, and in Chapter 6, where I discuss the interaction of clinical and scientific uncertainty in trials, drawing on the activities and behaviour that I observed at the ENABLE site.

During analysis I gave some consideration to issues of validity, which can be difficult to define and assess in qualitative research. Walsh and Seale (2018) suggest two forms of validation: triangulation, which involves checking findings against other sources, and member validation, whereby results are reported back to research participants to see if they agree with the conclusions that have been drawn (although they caution that both of these approaches are problematic). Triangulation makes a positivist assumption that the validity of a finding is called into question if it does not agree with other sources, and with this in mind although I compared the themes emerging in my analytical field notes to findings from the interviews and other fieldwork, the purpose of these comparisons was not to assess the validity of my analysis of the ENABLE trial as such, but rather to understand how the experiences and perspectives I observed there compared to the wider field of cell therapies. Member validation can be misleading, for instance if research participants lack knowledge or feel the results put them in a bad light. However, Rivas (2018) argues that it might be appropriate for research, such as mine, that aims to identify themes that are recognised or used by participants and peers, as it can be a useful way to check that you have picked up everything that is important to them and described it in a way they can relate to. For this reason I conducted member validation by presenting my findings to the ENABLE team at one of the last team meetings I

[5] I also applied this analytical framework to the notes I made of the other observational fieldwork I undertook during my research, which were constructed using the same approach as the ENABLE field notes.

attended, giving them the opportunity to comment and reflect on them. I was mindful of the limitations of this validation, however, and was careful interpreting the results, which I considered to be further data for analysis rather than an objective verdict on the validity of the findings.

Discussing findings with research participants might not necessarily confirm their validity, as such, but member validation can help to confirm the *authenticity* of ethnographic research (Walsh and Seale, 2018). Authenticity is far from the only criteria for evaluating ethnographic research, but it was certainly an important factor for my study given my aim of addressing not only a sociological audience but also biologists and health scientists such as the ENABLE team. Member validation was also an important step in starting to reflect on the implications of my findings, both in terms of the theoretical framework of co-production and in terms of recommendations for trial design. It thus contributed to the rich understanding of trial work which I had developed over the course of my fieldwork, which allowed me to observe how the meaning of a trial is structured, or constructed, not in the trial protocol or by regulators and policy-makers, but in the interactions that take place in the situated context of the trial itself. In conjunction with the characterization of the field provided by the dataset, and the range of perspectives and experiences described in the interviews, this allows me to examine the field at both a macro and micro level, and most importantly to understand how in the interactions between these two levels the science and social order of cell therapies are co-produced.

3. Cell therapies on trial: the current UK landscape

This chapter will present an empirically-informed account of the cell therapy trials landscape in the UK, examining both the characteristics of the trials being undertaken and the regulatory and policy environment in which they take place. In the light of Jasanoff's idiom of co-production, the discussion of cell therapy regulation that forms the first part of this chapter thus not only provides useful context for the rest of the thesis, it is also in itself a vital part of the story. With this in mind, I present an account of recent changes to the regulatory framework that is interwoven with data from interviews and observations, thereby shedding light on how these changes have affected the perceptions and actions of people working in the field. The second section of the chapter details the characteristics of current UK trials. This analysis uses both quantitative and qualitative data, allowing for a nuanced analysis that not only addresses *what* is being trialled and *how*, but also starts to engage with the question of *why* this might be the case, and the implications for current and future innovation in the field. This combined approach provides a 'broad-brush' understanding of the UK trials landscape that is both informative and reflective, complementing and contextualising the more detailed thematic analysis in subsequent chapters. Before this, however, I will present a short review of the current literature on regenerative medicine trials globally, demonstrating both how this has informed my research and how my findings will contribute to current knowledge.

3.1 Cell therapy trials: the global context

A number of studies published in recent years have documented the number and characteristics of cell therapy trials currently underway around the world. Most recently, Heathmann et al. (2015) found that as of January 2014 there were 1342 ongoing cell therapy trials registered on clinicaltrials.gov that met the British Standards Institute definition of cell therapies: "a therapy in which cells are administered to the body to the benefit of the recipient." Culme-Seymour et al. (2012) used similar criteria for defining cell therapies in their study, which reported

1925 cell therapy trials ongoing as of June 2010. Notably, both these studies include all cells used as a treatment, whether pluripotent, multipotent or fully differentiated 'adult' cells, and neither appear to have focussed solely on novel applications. In contrast to this, two other recent studies searched in particular for trials of novel stem cell treatments. Foley and Whitaker (2012) estimate that there were around 389 such trials underway in 2011 (excluding MSC trials), whereas Li et al. (2014) put the number at 1058 by January 2013 (including MSC trials). All of the above studies looked at cell therapy trials across the world, whereas one further study specifically examined ATMP trials in Europe, and found 318 trials, of which 78% were cell therapies (Maciulaitis et al., 2009).

The methodological differences between these studies make it difficult to draw direct comparisons between them, or to use them to track the development of the field over time. For instance, although Heathmann et al. report a significantly lower number of trials than Culme-Seymour et al. found four years earlier, it is not clear whether this represents a genuine decrease in the number of trials, or simply differences in methodological approach, such as the inclusion and exclusion criteria applied or the search strategy used. Likewise, Culme-Seymour et al. found that only 5% of trials involved permanent implantation of the cells, whereas Li et al. found that the majority of trials were 'regenerative' in nature (suggesting some sort of permanent implantation). Again, this difference may be due to the types of trial included and/or the way the trials were classified. Despite these methodological disparities, however, there are some common themes that emerge. Firstly, the majority of cell trials are at an early phase and are either publicly-funded or sponsored by small companies. Secondly, most trials are using relatively established cell types (MSCs and HSCs) as opposed to embryonic or pluripotent cells, and oncology, cardiology and neurology appear to be the only clinical areas where significant trials activity is taking place. Taken together, these studies paint a picture of a field still in its infancy, where expectations significantly outstrip current clinical reality. As Bubela et al. (2012) conclude, "while SC transplants are the standard of care for hematopoietic cancers and are gaining acceptance in the treatment of burns and corneal disorders, pioneering SC therapies directed at the regeneration of other

tissues and organs (that is, the promise of regenerative medicine) are few in number, use adult rather than embryonic stem cells, and are in the early stages of clinical investigation."

Although these studies provide useful context in terms of the number and characteristics of cell therapy trials, there are also significant limitations when using their findings to characterise the UK landscape, not least because they do not specifically focus on the UK. Furthermore, none of these studies is completely comprehensive, as they all rely on information from online trial registries, which, as acknowledged by Culme-Seymour et al., do not necessarily include all trials outside of the US. Indeed, the search strategies used may not necessarily identify all r*egistered* trials that meet the study entry criteria. For instance, Li et al. point out that Geron's ground-breaking trial was not picked up by their search strategy because the term 'stem cell' is not mentioned in the description of the trial. For those trials that are included, the analysis is based solely on information provided on trial registries, which is frequently incomplete or out of date, and, as noted by Culme-Seymour et al., does not always provide sufficient detail to categorise the treatment with any accuracy. Nevertheless, taken together these studies provide a useful backdrop for the detailed account of UK trials presented later in this chapter, which uses methods designed to overcome some of the limitations noted here (see Chapter 2 for more details). Before examining the specific characteristics of UK trials, however, I will discuss the regulatory and policy environment, and will consider how recent changes have affected innovation in the field, and in particular the conduct of trials.

3.2 The UK environment for cell therapy trials

Trials of medicinal products taking place in the UK are regulated under the European Clinical Trials Directive 2001, which was transposed into UK law as the Medicines for Human Use (Clinical trials) Regulations 2004. Underpinning the Clinical Trials Directive is a requirement for all trials to be conducted in accordance with Good Clinical Practice (GCP): "an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects" (EMA, 2016). There is also a requirement for all Investigational Medicinal

Products (IMPs) to be manufactured to Good Manufacturing Practice (GMP) standards in a licensed facility. The Advanced Therapy Medicinal Product (ATMP) regulations, which were introduced in 2007, mean that the majority (although not all) of the novel cell therapies being developed and trialled in the UK are classed as medicinal products, and therefore fall under all of these regulations. Additionally, all clinical trials in the UK (not just those of medicinal products) fall under the scope of the Research Governance Framework for Health and Social Care 2005, which concerns all research taking place in the NHS. From a practical and logistical perspective, the UK clinical research environment is also increasingly shaped by the National Institute of Health Research (NIHR), which was set up in 2006, and the UK Clinical Research Network (CRN).

The scale, speed and scope of these changes mean that the environment for UK cell therapy trials is almost unrecognisable from that which existed when many of them were being planned. The 'rules of the game' have completely changed over the past decade and a half - in the words of Interviewee 1: *"if we were starting now, would we be allowed to do what was done 20 years ago? Probably not."* This section of the chapter will examine the environment in which cell therapy trials take place in the UK, beginning with an overview of the specific ATMP regulations, before moving on to discuss the regulations for clinical trials more generally. The section concludes with a review of the key policy initiatives and issues that are currently shaping the field, and a consideration of how these might affect its future direction.

3.2.1 Regulatory framework

There are two key factors that determine whether a cell therapy is designated as an ATMP: whether the cells have been *substantially manipulated* and/or are not being used in their original function (*non-homologous use*). There are four categories of ATMP: tissue engineered products, gene therapy products, somatic cell therapy products and combined products (EMA, 2015c). Most cell therapies classified as ATMPs fall within the somatic cell therapy category (see Figure 2.1 overleaf).

Figure 2.1: Definition of Somatic Cell Therapy (EMA, 2015c)

> (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
>
> (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

ATMPs are treated as medicinal products, which means that they are subject to the same regulatory framework as pharmaceuticals. This has a number of implications, including the requirement for marketing authorisation applications to be supported by significant clinical trials data demonstrating safety and efficacy, and clinical trials to be approved and inspected by the national competent authority, which in the UK is the Medicines and Health Research Authority (MHRA). Medicinal products also must be manufactured to GMP standards using appropriate clean-room technology, and require sign-off by a Qualified Person (QP) (Abou-El-Enein et al., 2013). Access to these treatments is restricted in the same way as pharmaceuticals, meaning that an ATMP must have marketing authorisation or clinical trial authorisation in order to be used in the clinic (although the Hospital Exemption/specials route, discussed below, does allow for limited use in an individual hospital setting).

Classification as an ATMP can have significant implications for the development of a therapy, as shown by Faulkner's work on the development of ACI, which was initially treated as a medical device but once classified as an ATMP became subject to a different regulatory regime that until then had been more associated with pharmaceuticals (Faulkner, 2009). Unsurprisingly in this context, many interviewees reflected on how relevant/appropriate the ATMP classification is for their specific

product. For instance, Interviewee 9 felt that he had been caught up almost by accident in regulations primarily aimed at a different area:

> "I think the ATMP regulations probably came in because of genetically modified materials and stem cell work, neither of which ours is anywhere close to." (INT9)

Another interviewee reflected on the subjectivity involved in judging whether a therapy involved non-homologous use of cells:

> "The regulation, both in the US and Europe, allows in one operative procedure an exemption from being a medicine. But it also has to be homologous - and the question is, what's homologous use? So for example, the cardiac stem cell story - lots of people have been injecting bone marrow cells into hearts, in January 2013 the Committee for Advanced Therapies decided that bone marrow stem cells do not normally reside in the heart, therefore this is not homologous use, therefore it's a medicine. That stopped a ton of trials." (INT12)

The concept of 'substantial manipulation' is also contentious, because although any expansion of cells is automatically considered substantial manipulation, other processes are less clear-cut. For instance, at a meeting to discuss the challenges associated with cell processing, there was a discussion about the fact that enzyme digestion is considered substantial manipulation. One delegate mentioned that pancreatic islets are an exception to this and was asked whether there was any biological basis for this exception (i.e. whether islets had been shown to be less affected by enzymatic digestion). He replied that he didn't think so, and the exemption was more likely due to the number of islet treatments already being used, and perhaps successful lobbying to avoid these treatments being reclassified as ATMPs (Field notes 23/09/15). This example demonstrates not only the confusion and debate surrounding the classification of specific cells, but also the perception that factors other than clinical or scientific considerations have an impact on regulatory decisions.

Further complexity, and contingency, is created by the fact that the ATMP regulations have been interpreted differently by the various member states of the European Union. As Pearce et al. (2014) note, "there are substantial differences in the definition of ATMPs and in the approved manufacturing environment", meaning that both the classification of an ATMP and the implications of this classification are not consistent throughout the EU. This has significant implications for anyone developing products for distribution in Europe, and it also affects any clinical trial taking place in more than one member state. A number of interviewees commented on these inconsistencies, for instance Interviewee 12 highlighted the different interpretations of non-homologous use:

> "The definition of non-homologous is one of the big problems internationally … so you'll have something that's non-homologous in one regulatory area, but homologous in another." (INT12)

Another interviewee explained the complications caused by the fact that the treatment they were testing was classified as an ATMP in Germany, but not in the other countries taking part in the trial:

> "The Germans … because it was a medical product or whatever it is, they had to get a special licence for it, you know. They had to do tons of microbiology and tons of experiments and collect lots of data, which none of the rest of us were doing." (INT7)

These examples highlight the complex and disjointed nature of the regulatory framework within which cell therapies are being trialled, and we shall see throughout this thesis the difficulties that this can cause.

The introduction of the ATMP regulations significantly increased the administration, cost and time required to undertake clinical trials of cell-based therapies. However, although this more restrictive framework makes the translation of cell therapies more difficult, none of the interviewees expressed any dissatisfaction with the regulatory framework overall, and all were in agreement with the principle of cell therapies being held to a higher standard of evidence than previously. Comments made about difficulties experienced with the regulations were often

qualified with an acknowledgment that their basic principles were 'right' or 'reasonable', and there was general acceptance that the process of proving these therapies to be safe and effective was both achievable and desirable. Interviewee 12 went as far as to defend the ATMP framework against criticisms that it is delaying clinical adoption of cell therapies:

> "One of the things that CAT has been accused of is you've only got three products in Europe that have got marketing authorisation, this just proves that the regulatory environment doesn't work. Well if you go back to the last sea change technology - that was biologics, monoclonal antibodies - from the invention of monoclonal antibodies through to the first licensed medicine was 24 years. OK, within five years, less than that, within three years of the ATMP regulation being published we have three licensed, four licensed medicines." (INT12)

It seems, then, that there is general support for cell therapies being subject to regulation and oversight, but it is the specific nature of these regulations, and the practical impact they have, that are often viewed as problematic.

The challenges caused by ATMP classification can be avoided in certain circumstances, because although ATMPs generally require either a marketing or clinical trial authorisation, the legislation allows for the exemption of treatments that are "prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient" (Cuende et al., 2014). Inevitably, this exemption has been interpreted differently by the various member states, with the terms 'custom-made', 'industrial process' and 'non-routine' all being open to interpretation. In the UK, therapies must be prepared within the same hospital to be eligible under what is known as the Hospital Exemption (HE), and these products do not require a QP to sign them off (Cuende et al., 2014). Although providing the least restrictive of the regulatory options for producing cell therapies, at the time of writing there was only one site in the UK known to be producing cells

under HE. It does not, therefore, appear to be a significant route for the development of such treatments, a conclusion that is supported by the fact that many interviewees had not heard of it. For instance, when Interviewee 4 (a clinician) was asked if he had considered applying for it, he replied: *"I don't know, what's a Hospital Exemption licence?"*

The relative obscurity of HE in the UK may be partly due to the existence of an alternative - the so called 'specials' route, which provides a similar framework for the delivery of medicinal products without a marketing authorisation (MHRA 2014). This is more restrictive than HE in some ways, for instance the requirement for a QP to sign off batches of product. However, a specials licence provides greater scope for the delivery of cell therapies, because the use of the product is not restricted to the hospital where it was prepared, and indeed it makes it possible to import and export unlicensed medicinal products (Cuende et al., 2014). There is no centralised data available on the number or type of cell therapies being delivered under specials licences, or how many patients have been treated. However, there are a total of 26 sites with licences to manufacture cell therapies for human use (MHRA, 2015), and a number of interviewees described such cells being in regular use. For instance, Interviewee 6 (who runs a small lab with a specials licence) described the process of providing cells to clinicians around the country:

> "Customers come back over and over again, so we're selling them. Not at a profit of course - you're not allowed to do that. But we're selling them to Bristol, Birmingham, Manchester, Leeds, Sheffield, a lot - all over the country." (INT6)

It appears, then, that although it is not possible to quantify exactly how many cell therapies are delivered using specials licences, it is certainly a significant route for the delivery of cell therapies in the UK (alongside clinical trials).[6]

[6] For the purposes of clarity, I will use the term HE to refer to both the Hospital Exemption and specials routes for the remainder of the thesis, because although there are slight differences between them as highlighted here, these do not significantly affect my analysis.

The interview data demonstrates divergent views on how HE, clinical trials and marketing authorisation might, or should, align with each other. Some cell therapy developers feel that their treatments should only be tested in clinical trials, for instance Interviewee 5 explained that he had decided to go straight into clinical trials, saying of HE: *"it would be possible, but we haven't gone that route at all."* For others, HE might be used *alongside* a clinical trial to ensure that patients who are ineligible for the trial, or whose cells fail to grow, can still be treated. For instance, Interviewee 1 explained that the exact specification of the trial treatment was too toxic for the poorliest patients, but their specials licence meant that these patients could still be given a less invasive version outside of the trial:

> "We have treated some patients off-trial like that, because they just weren't, they just weren't well enough. And it does seem to work, so …" (INT1)

Other interviewees described HE as being a precursor to, and a vital enabler of, a full-scale trial, with one interviewee explaining that:

> "It's been crucial really - I mean it's not the way to develop a product, but for this type of ATMP, or regenerative medicine, activity it's probably desirable. If you can, and you can do it ethically, then it's desirable because you learn so much not only from the patients but also from doing it to the right kind of standards." (INT17)

In contrast to this, others viewed it as a follow-on from the trial, essentially as an alternative for products that were not suitable for the marketing authorisation route. For instance, Interviewee 12 explained:

> "Our aim in our current trials is to make the process of manufacture so streamlined and so reproducible and so easy that you can add it into a contract manufacturer that will manufacture it for payment, full reimbursement and profit. But they can't advertise it, all they can say is we have the capacity to make this. And then surgeons round the country can say I need [treatment name] for my patient,

> and they can contact the contract manufacturer and say I want you to make this for me - that's being prescribed that way rather than advertised that way, and therefore you can manufacture an unlicensed medicine." (INT12)

Clearly, then, there is a range of different views on the utility and validity of HE and specials, and how they should interact with trials; I will return to this in more detail in the discussion of uncertainty in Chapter 6, and views of evidence in Chapter 7.

3.2.2 Clinical research environment

In addition to the specific regulations governing regenerative medicine, cell therapy trials are also subject to the generic framework which regulates the conduct of all clinical trials. The Clinical Trials Directive was intended to streamline the process of gaining approval for trials in different member states, protect the interests of patients, and ensure the robustness of data collected (European Commission, 2001). Despite being intended to improve efficiency, these regulations in fact increased the administrative burden of conducting trials, increasing the cost and time needed to conduct a trial, and resulting in a marked decrease in the number of applications for new trials (NHS European Office, 2014). A number of interviewees referred to difficulties caused by the new regulations - although these difficulties generally related to the rules changing mid-way through a trial, rather than the regulations themselves. For instance, Interviewee 4 described how the changes exacerbated the fact that he was already working in unfamiliar territory:

> "We started to put the proposal together at just the time when the European Clinical Trials directive came in. So not only was I sort of setting out on something I knew nothing about, it was in a terrain that was going to completely change in the next few years." (INT4)

As with the ATMP regulations, the Clinical Trials Directive has not been interpreted consistently throughout the EU, as Interviewee 4 went on to explain:

> "We were learning as we went along, and every country introduced the Clinical Trials Directive at a different speed, slightly different local regulations." (INT4)

These quotes suggest that the introduction of new clinical trials regulations, which happened to coincide with the ATMP regulations being introduced, created uncertainty and confusion that may have hampered many cell therapy trials being set up during this period.

There is growing international recognition of the difficulties associated with running clinical trials in general, and in particular early-stage trials, and the OECD (2013) argues that "the need to re-assess and strengthen the international clinical trial paradigm has never been greater." Following the Road Map Initiative for Clinical Research, which brought together representatives of academic and not-for-profit organisations to discuss how the European Trial Directive could be improved (OECD, 2013), new EU trials regulations were brought in in 2014 (NHS European Office, 2014). The new regulations aim to further streamline the process of approval for new trials, which should certainly be beneficial for cell therapy trials taking place in multiple European countries. The other improvements, however, including a lighter regime for trials of medicines that are already authorised and pose minimal risk, are unlikely to be relevant to many cell therapy trials in the short or medium term. Furthermore, although streamlining the trial regulations between EU member states will ease some of the administrative burden, the majority of the concerns raised by interviewees related to inconsistencies between member states around the implementation of the ATMP and GMP regulations, which will not be resolved by the new trials regulations. It appears, therefore, that even if successful, the changes to the EU Trials Directive will not have a marked impact on how easy it is to set up and run multi-country cell therapy trials.

As well as the regulatory framework determined by the Clinical Trials Directive, another important factor affecting clinical trials in the UK is the clinical research environment. The UK is distinctive in having a National Health Service that provides coordinated healthcare services that are free at the point of use, providing a centralised structure within which to conduct clinical research. This should theoretically make the UK a competitive place to conduct clinical trials, and the establishment of the NIHR was intended to capitalise on these strengths by providing a framework for clinical research, and to embed the principle that "clinical research

is, and has always been, at the very heart of the NHS" (NIHR, 2015). This is the rationale underpinning the CRN, which provides an infrastructure intended to facilitate research by supporting clinical studies that are 'adopted' onto its portfolio. This is primarily achieved through the provision of resources, for instance by funding dedicated research nurses or providing specialist equipment.

A number of interviewees reported receiving CRN support, and in some cases this support was seen as making a significant difference to the trial. Interviewee 3, who was working on a multi-site trial, described the improvements seen at one of the sites once dedicated support was provided through the local CRN:

> "In Nottingham we have LCRN nurses who are involved … and that only came on board mid-way through the trial. And that made a big difference." (INT3)

The same interviewee described the effort that the Principal Investigator (PI) put into securing this support in a rapidly changing clinical research environment:

> "Trying to literally leap onto that bandwagon as it was zooming past at a very fast pace is down to his Maserati skills I think." (INT3)

Other interviewees placed less importance on CRN support, which in some cases may have been because their trials were not eligible. In some cases, however, even those who were eligible didn't expect the support to be significant:

> "That will I think provide us with a small amount of additional support if the trial is adopted. I'm a bit vague about this because I haven't got there yet, but it's quite a small amount of support I believe." (INT5)

CRN support is thus perceived by some as an important factor in the success of a trials, and worth putting effort into securing, whereas for others it is viewed as either irrelevant or insignificant.

Another aim of the CRN is to improve recruitment into trials, both to improve the efficiency and competitiveness of UK trials, and because access to trials is seen as being of value to patients. Although in principle this applies to both publicly and

industry funded trials, the emphasis on competitiveness suggests a distinctly commercial perspective. As Will (2011) argues, this "asks NHS providers to act almost as CROs, bringing together different actors to ensure efficient recruitment for trials funded by industry." In this context, it is interesting that although many interviewees described challenges associated with trial recruitment, Interviewee 11 (a commercial sponsor) was the only one to mention the CRN in connection to recruitment. He explained that one of his company's motivations for opening trial sites in the UK was the existence of a disease-specific CRN that they believed would make recruitment easier. In reality, however, the UK sites struggled to recruit (in some cases doing worse than sites in other countries), and he felt that this might in part have been due to the number of other portfolio studies taking place at these sites at the same time. The CRN also aims to improve the conduct of trials through training and shared expertise, but this was not mentioned by any interviewees, even when prompted. It appears, then, that the only significant way in which the CRN supports cell therapy trials is through the provision of resources, and that even this is only relevant or substantial for a subset of trials.

3.2.2 Recent policy developments

Taken together, the ATMP regulations and the EU Clinical Trials Directive have significantly increased the administrative burden of conducting cell therapy trials, and this is certainly an important factor in the perceived barriers to innovation in the field. In 2013, the House of Lords Science and Technology committee conducted a review of Regenerative Medicine in the UK, and the resulting report concluded that the UK has a number of strengths, including a strong basic science base, a unified healthcare system, experienced blood and transfusion centres, and experienced clinicians and scientists, but that translation to the clinic is being hindered by regulatory complexity (House of Lords, 2013). Alongside a suggestion that the clinical trials process for regenerative therapies be reviewed, the report also proposed the creation of a regenerative medicine stream in the Clinical Research Network, with a view to overcoming some of these hurdles (O'Dowd, 2013). The government response to the report did not action this recommendation, but instead set up Regenerative Medicine Expert Groups to examine different aspects of the regulation of Regenerative

Medicine (Department of Health, 2013). The remit of these groups is narrower than the envisaged CRN, both in terms of time - the RMEG involved a one-off assessment and report that was delivered in December 2014 - and in terms of reach. In the words of Interviewee 12, who sat on one of the RMEGs:

> "The remit for the expert groups was really quite narrow - they were to look at whether the regulatory environment was fit for purpose for this particular application, and if not what ... options there are for change." (INT12)

In contrast, a CRN dedicated to regenerative medicine, if it followed the format of the other CRNs, would have had provided a much broader range of support for trials, including regulatory advice, training and the provision of resources to help with recruitment.

In principle, then, it appears that the government response to the House of Lords report fell some way short of implementing the changes that were recommended. In practice, however, a dedicated regenerative medicine CRN might not have been the most appropriate way to address these obstacles for a number of reasons. Firstly, as will be discussed later in this chapter and in Chapter 5, there are actually very few challenges that are common to all cell therapy trials. Rather, the challenges faced are largely dependent on the specifics of the disease, the characteristics of the treatment, and the institutional setting where the trial takes place. Indeed, trialists themselves often don't associate their work with 'cell therapy' or 'regenerative medicine' at all, but tend to have much greater affinity with the clinical area, as these quotes demonstrate:

> "I'm not sure that it really is regenerative medicine, although we do kind of tend to often get lumped in to that category … If you asked me to pick one of those labels it would be clinical immunologist." (INT5)
>
> "No, it's more of a clinical level ... there's probably very little communication with other specialities that use cellular therapies." (INT6)

> "There's not really a broad regenerative medicine collegiality, all my, my collegiality, you know - it's the [physiological] system." (INT2)

In this context, and particularly given the very small number of cell therapy trials currently underway, it is hard to see how a regenerative medicine CRN would be of more help than the existing disease-specific CRNs, or the new regional framework that is being introduced to replace them. This suggests that whilst dedicated support for cell therapy trials would be valuable, this would perhaps function best if it were provided alongside the existing CRN framework, rather than within it.

Another factor which suggests that a dedicated CRN might not the best vehicle for delivering the support needed to facilitate cell therapy trials is the fact that, as I discussed earlier, although a number of interviewees mentioned receiving support from the CRN, this was always in the form of resources (specifically research nurses to help with recruitment and trial coordination). No interviewees mentioned their CRN being helpful in terms of providing expertise or regulatory advice, which are two of the biggest challenges faced by cell therapy trialists. Support in these areas, when it was mentioned, came from a variety of other sources (including trials units, commercial contacts and regulators) rather than from the CRN. This suggests that although interviewees might have welcomed a more 'one-stop-shop' service providing advice and support for cell therapy trials, there is nothing in their experiences to suggest that the CRN in its current form would be the most appropriate way to provide this. Another, potentially more appropriate, initiative for providing centralised support for cell therapy trials is the Cell and Gene Therapy Catapult (CGTC), which was established in 2012 (as the Cell Therapy Catapult) with the aim of helping the UK "be a global leader in the development, delivery and commercialisation of cell therapy" (CGTC, 2016). The Catapult supports developers of cell therapy products by providing them with clinical, technical, regulatory and business expertise, and is also planning to open its own manufacturing centre in 2017, which "will be used by *companies* for the manufacture of late phase clinical trial and initial *commercial* supply of advanced therapeutic medicinal products including cell and gene therapies" (CGTC, 2016).

With its specific focus on cell therapies, and expertise in all aspects of the regulatory and logistical requirements for trials, the Catapult is potentially a much more suitable vehicle than the CRN for providing the kind of support called for in the House of Lords report. There are, however, aspects of the Catapult's remit that might limit its utility for many trials. In particular, as can be seen from the mission statement quoted above, its focus is primarily on the commercial development of cell therapy products, and in fact many interviewees working on publicly-funded trials felt that its activities were largely irrelevant to them. For instance, Interviewee 10 (a clinician) questioned whether the Catapult would have any interest in the structural issues he had experienced in the NHS:

> "I'd be interested to know what the stem cell catapult [sic] is doing in this area ... I suspect it's not looking at the NHS infrastructure issues." (INT10)

In a similar vein, Interviewee 6 (the manager of a hospital-based cell lab) doubted that the Catapult would be interested in her work because it was too small-scale and uncommercial:

> "I don't think my department - any hospital department - could reach any level that we'll be able to sell a medicine … so that's what Catapult want isn't it, they're not bothered about the NHS." (INT6)

In general, then, it appears that the Catapult's aims are not perceived to be aligned with the development of small-scale cell therapies in an NHS hospital setting.

This lack of relevance also extended to other aspects of the Catapult's activities, in particular the development of a centralised manufacturing model. At best, this was perceived to be irrelevant for many cell therapies - for instance, Interviewee 2 thought that it would never be practical for the kind of therapy he was developing:

> "It may be that, you know, a common service centre like the Catapult will be right for, maybe for things like cardiac where you're just taking the stem cells and processing them for delivery in a surgical clinic. Certainly for the sort of stuff we're doing in the [disease area], where it's not just a cell but it's got to grow and

> integrate and connect, it's a whole package so you can't really take it off the shelf." (INT2)

At worst, the Catapult's new manufacturing facility was perceived to be a possible threat to localised cell manufacturing, for instance a number of ENABLE team members expressed concern that the increased prominence of the centralised model could lead to funds and expertise being diverted away from therapies that require local manufacturing.

These findings suggest that the Catapult is in a good position to facilitate trials of all cell therapies, and not just those being developed commercially, but in order to do so it would have to engage more effectively with the publicly-funded settings that make up the majority of current cell therapy trials. There is some evidence that this engagement has been lacking thus far - for instance, Interviewee 10 criticised the Catapult for not having shown any interest in his experience of running a cell therapy trial:

> "Nobody from the Catapult has ever contacted me … I think wouldn't you have something to learn from our experience?" (INT10)

This was not necessarily a universal experience, however, and it must be noted that when my interviews were conducted the Catapult was a relatively new organisation, and furthermore most interviewees had already successfully set up a trial and were therefore not at a stage where they needed the Catapult's support. Certainly, there is some indication that those who are still in the early stages of the process are keen to understand what the Catapult could offer them. Interviewee 16 (who was still undertaking pre-clinical work) explained that he had approached the Catapult but found their advice was not yet relevant to him because *"at the moment my problem is not quite 'catapultable'"*. However, he expected to work with them in future when his therapy was ready for a Phase 1 trial.

In addition to these UK-specific initiatives, there are also developments at an EU level that aim to speed up the process of getting cell therapies into the clinic. For instance, adaptive licensing (AL) is being explored as a means of ensuring patients

have access to innovative new treatments as soon as possible. AL is defined by the European Medicines Agency (EMA) as "a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations" (EMA, 2014). According to Eichler et al. (2015) two key factors are driving the move to AL: patient demands for access to promising new treatments, and scientific progress leading to the fragmentation of treatment populations, which makes it harder and slower to assess safety and efficacy using traditional trials processes. In conjunction with AL, risk management systems (RMS) are increasingly being used as a means of overcoming the 'valley of death' economic issues facing developers of innovative biomedical treatments. The UK has been at the forefront of these developments, introducing schemes where, for instance, the manufacturer reimburses drug costs if long term endpoints are not met, or for patients who don't respond to the treatment, as well as cost-limiting schemes such as cost discounts, dose capping and free first cycles to limit the initial outlay on experimental treatments whilst still providing some reimbursement for manufacturers (OECD, 2013).

Both AL and RMS would seem to offer useful possibilities for developers of cell therapies, however there was little evidence of my interviewees being aware of these opportunities. This lack of awareness may be in some part due to the relative recency of the policies, and to the fact that many interviewees had only limited knowledge of the regulatory environment. However, it is notable that the only interviewee who made any reference to either AL or RMS was a commercial cell therapy developer, indicating perhaps yet another area of policy that is more aligned to commercial innovation than academic or clinical development. A lack of commercial motivation or awareness amongst many trialists could mean they have limited interest in exploring new approaches to licensing and reimbursement, or don't feel that these would be relevant to their situation.

It may be that AL and RMS are most relevant to commercial cell therapy development, but there is some indication that even here, they are unlikely to be

panaceas. For instance, Interviewee 17 was unsure whether such schemes would be right for his company (a small spin-out with a relatively niche product) because of the likely costs involved in the process:

> "The accelerated licensing scheme ... I'm not convinced that's necessarily right for us, because it may mean iterative changes in what we do as we get more data and more application, and each one of those iterations of a marketing authorisation is tens if not hundreds of thousands of pounds. So it might look great to get there quickly, but then we might be condemning ourselves to any iterations are going to cost us a fortune. So as no-one's been through it yet we don't know how it will work." (INT17)

It seems, then, that although there are many promising developments and policy initiatives, the regulatory and clinical research environment for cell therapies in the UK remains challenging. To fully understand both the reasons for and the implications of these challenges, it is necessary to examine the characteristics of UK cell therapy trials in more detail, and this is the focus of the remainder of this chapter.

3.3 Characteristics of UK trials

There were 44 cell therapy trials that met my inclusion criteria at the time I produced the trials dataset (April 2016), which is slightly lower than the 51 reported on the 2015 Cell Therapy Catapult database. This difference is due to the exclusion of three trials not showing on any trial registry, one study where the cell therapy was not the subject of investigation, one which was investigating an established cell transplant condition, one observational study and one duplicate record. Of the 44 trials in the dataset, one (2%) was registered as closed with follow up complete, and three (9%) were showing as suspended (interview data on one of these trials suggests that it is unlikely to resume in the near future). In total, then, there were 40 ongoing trials at the time I completed the dataset, of which 24 (55%) were recruiting patients, six (14%) were in set-up and eight (18%) were in follow-up.

These figures suggest that cell therapy trials activity in the UK is very limited at present, and the number of regenerative therapy trials is even smaller, as we shall

see later in this chapter. This fact was emphasised by the head of one of the UK's main centres for regenerative medicine, who explained that although the research councils spend around £100m a year on regenerative medicine, the vast majority of this is on basic pre-clinical research, with only 7% spent on clinical trials (Field notes 01/05/2014). Research council spending is particularly pertinent because the majority of trials are publicly-funded, with only 12 (27%) having commercial involvement. This is in line with the global picture for cell therapy trials reported by Li et al. (2014), but is at odds with the characteristics of clinical trials overall (i.e. of all types of treatment) - for instance, in the UK commercial trials outnumber those funded publicly by a ratio of 2:1 (Will, 2011).

The limited number of cell therapy trials might be considered somewhat surprising given the amount of basic science being done in this area, and the media coverage it attracts. Interviewee 10 commented on this:

> "I think the first thing I was surprised at … when we went to set this study up, actually this might be in the newspapers every day [but] there are very few stem cell studies set up in this country …. there's all these people going on the news talking about stem cells, but the vast majority of them have never done a clinical trial with them." (INT10)

He went on to explain that this had implications for setting up his own trial:

> "We had to set everything up sort of from scratch to be quite honest." (INT10)

The absence of other trials to learn from can thus in itself be a barrier to more trials being conducted, and this is further compounded by the fact that many trials are sponsored by academic institutions that have little experience in the area, as explained by Interviewee 2:

> "And they are largely academic-led, the sponsors tend to be academic institutions - they've never sponsored trials before, they're learning very rapidly." (INT2)

I shall return to this issue of expertise, and the challenges experienced when running trials in academic settings, in Chapters 4 and 5, which examine the 'doing' of cell therapy trials in practice. Before that, however, the rest of this chapter will present a detailed account of the UK trials dataset, first examining the types of treatments being trialled, and then going on to look at the trial methods being used.

3.3.1 Therapies being trialled

Clinical indications

Table 3.1 (overleaf) details the clinical areas where cell therapies are currently being trialled in the UK, based on the code frame used by Li et al. (2014). Cancer, neurology and cardiology are the three most dominant clinical areas for trials, with cancer accounting for 27% of all UK trials (although this falls to 9% when patient numbers are taken into account). This is broadly in line with the global picture reported by Li et al., although cancer appears to be relatively more dominant in the UK, representing 27% of trials in comparison to just 9% globally.[7] It is interesting to consider this data in the context of the four cell therapy products that have gained marketing authorisation in Europe. Only one of these (Provenge, a treatment for prostate cancer) falls into the clinical areas where most trials activity is taking place, whereas two (MACI and ChondroCelect) are treatments for cartilage defects, which represent just 4% of UK trials, and the other (Holoclar) is a treatment for eye disease, which represents 7% of UK trials. In total, then, 75% of the cell therapies that have successfully applied for marketing authorisation represent clinical areas that make up just 11% of trial activity. It is also interesting that neurology is such a significant area for trials, given that CNS conditions are perceived to be one of the most challenging areas for regenerative medicine.

[7] This may partly be due to the methodological differences between the two studies, and in particular the fact that the Li et al's study excluded adoptive T-cell cancer treatments.

Table 3.1: UK cell therapy trials by clinical area

Clinical area	Trials		Patients	
	Number	%	Number	%
Cancer	12	27%	211	16%
Neurological disease	8	18%	220	17%
Cardiovascular disease	5	11%	349	27%
Gastrointestinal disease	5	11%	120	9%
Eye disease	3	7%	56	4%
Other	2	5%	20	2%
Immunodeficiency	2	5%	20	2%
Cartilage disease	2	5%	124	10%
Liver disease	1	2%	81	6%
Bone condition	1	2%	60	5%
Systemic rheumatological disease	1	2%	12	1%
Skin condition	1	2%	10	1%
Kidney condition	1	2%	12	1%
Diabetes	0	0%	0	0%
Organ transplant-associated	0	0%	0	0%
Lung disease	0	0%	0	0%
TOTAL	**44**	**100%**	**1295**	**100%**

The dominance of cancer trials can be linked to a number of factors, including the fact that cancer research is generally well-funded and has a well-established research platform that means clinical trials are embedded in the overall 'practice' of treating cancer (P. Keating and Cambrosio, 2007). Additionally, recent successes have generated significant commercial interest in the area, as explained by Interviewee 5:

> "CAR t-cells in particular are being heavily commercialised at the moment, because some really remarkable results have been generated." (INT5)

This combination of an existing infrastructure for research, availability of funding and promising early results suggests that cancer is likely to remain at the forefront of cell therapy trials. In some ways, the success of cancer trials could be beneficial to the field as a whole. Many of the logistical issues of working with cells will be common to all clinical areas, so learnings from early cancer trials can be applied to other cell therapy trials in the future. Likewise, success in one clinical area may generate enthusiasm, and possibly funding, in other areas, as suggested by Interviewee 9:

> "Cancer immunotherapy has been around for quite a few years, and that's started to work … so you're getting some very strong messages out of cancer, which I think is encouraging the rest of us." (INT9)

However, the benefits of cancer trials 'leading the way' should not be overestimated, because other clinical areas will have distinctive characteristics that mean they might need a very different approach, as Interviewee 7 explained:

> "A lot of the people I talk to in America, for example, will say 'yeah, we do this type of thing with cancer' - but I say 'well it's very different in cancer.' Because, as I said, normally these therapies are used in people where there's a very clear outcome - you're alive or dead, you can monitor it very easily because you can look at the tissue, the tumour size. Here we're trying to see things in the brain, which we don't have access to." (INT7)

It may be, then, that some aspects of cancer trials are distinct from other types of cell therapy, and thus approaches that work for cancer may have limited value for trials in other areas.

The interview data also provides some other interesting insights into why cell therapy trials might be more successful in a particular clinical area. One common issue was the perceived risk of the procedure; for instance, Interviewee 5 explained

that this was a factor in choosing to test the therapy in a cancer involving an accessible tumour:

> "It's an opportunity to de-risk a potentially hazardous cell therapy, because we can think about implanting those cells directly into the tumour to minimise the systemic absorption of those cells." (INT5)

This quote also highlights another factor that makes certain clinical conditions more attractive for cell therapy development, which is the ease of delivering the cells. Although the risk and simplicity of the procedure are clearly important, however, they are not decisive, as there are a number of trials being undertaken that involve relatively high-risk procedures, such as injecting cells into the brain. Another important factor is the familiarity of the procedure to the clinicians involved, as exemplified by these quotes about cell therapies in haematology and osteoarthritis respectively:

> "Yes, it's a major change, but still putting things back into patients, which is what they're already doing in terms of transplants and such like." (INT9)
>
> "Chondrocyte transplant - so moving bone round the body using allografts, transported bone, regeneration of bone - all of these things have been happening over two decades." (INT15)

It appears, then, that an element of familiarity also plays a role in determining the clinical areas where cell therapy development is more likely to succeed.

Types of cells

Table 3.2 (overleaf) details the types of cells being used in UK cell therapy trials (again adopting the code frame used by Li et al.), and shows that hematopoietic and mesenchymal cells account for three quarters of all treatments being tested. Notably, only 4 (9%) of the trials in the dataset involved embryonic cells, all of which were commercial trials. These findings are in line with Li et al., who found that hematopoietic and mesenchymal cells represent 80% of global trials. However, their research suggested an even split between the two cell types, whereas in the UK hematopoietic trials outnumber mesenchymal trials by a ratio of 3:1. Again, this

difference will partly be due to their exclusion of adoptive T-cell treatments, because Table 3.3 demonstrates that T-cells make up more than half of the hematopoietic trials in the UK, and nearly a third of all cell therapy trials.

Table 3.2: Types of cells used in UK trials

Type of cell	**Number**	**%**
Hematopoietic (whole marrow, CD34+, CD133+ or mononuclear fractions)	25	56%
Mesenchymal	8	18%
Embryonic	4	9%
Other	4	9%
Neural	2	4%
Limbal	2	4%
TOTAL	**45**	**100%**

Table 3.3: Breakdown of hematopoietic cells (based on description given in protocol)

Type of hematopoietic cell	**Number**	**% (of all trials)**
T-cells	14	32%
Bone marrow cells	3	7%
CD133+ cells	3	7%
CD34+ cells	3	7%
Mononuclear cells	2	5%
Expanded hematopoietic stem cells	1	2%
TOTAL	**26**	**59%**

The prevalence of hematopoietic cells in UK trials reflects the fact that cancer is the most common clinical area, as all the cancer trials use hematopoietic cells. It is also important that hematopoietic stem cell transplant is a well-established procedure, meaning that there are existing facilities, infrastructure and experience that can be used for trials.

Table 3.4 shows that around a third of UK trials involve allogeneic cells, which is broadly in line with the global breakdown reported by Foley and Whitaker in their 2012 review and Li et al.'s 2014 study. Interestingly, there is a relatively even split between allogeneic and autologous cells in company-led trials in the UK, although clinician-led trials are dominated by autologous treatments. There is also a relatively even split between allogeneic treatments that are delivered as products and those that require more complex surgical procedures, which does not align with the conventional view of allogeneic cells having an 'off the shelf' business model that makes them a more appealing commercial proposition.

Table 3.4: Autologous and allogeneic treatments broken down by mode of delivery and type of trial

	Autologous		**Allogeneic**		**TOTAL**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Product	19	61%	6	46%	25	57%
Procedure	12	39%	7	54%	19	43%
TOTAL	**31**	**100%**	**13**	**100%**	**44**	**100%**
Industry-led	6	19%	6	46%	12	27%
Clinician-led	25	81%	7	54%	32	73%
TOTAL	**31**	**100%**	**13**	**100%**	**44**	**100%**

There is a variety of allogeneic cell types being used, including T-cells (four trials), embryonic cells (four trials), neural cells (two trials), MSCs (two trials) and limbal stem cells (one trial). Notably, these include pluripotent, multipotent and fully-differentiated 'adult' cells (i.e. not stem cells). The interview data suggests that the difficulty of getting a trial approved is not necessarily determined by whether the cells are allogeneic, but is more specifically linked to the cell type and the mode of delivery. Allogeneic MSCs, for instance, appear to be fairly straightforward from a regulatory perspective, despite being multipotent and classified as ATMPs. When asked whether using allogeneic cells made it harder to get a trial approved, Interviewee 10 (who had conducted a trial using allogeneic MSCs) replied:

> "No ... I don't think so. I'll be honest with you - of the entire trial there in the UK the only, the hardest thing was trying to get the sites up and going, it just took us forever. Not the MHRA." (INT10)

The same was true for a trial using allogeneic neural cells sourced from aborted foetuses, described by Interviewee 7. In this case the cells were not manipulated and so not classed as an ATMP, and the cell processing did not appear to have caused any regulatory difficulties. However, the procedure for delivering the cells was relatively complex, and it was here that regulatory barriers had been experienced. It seems, then, that a number of factors affect how difficult it is to set up a trial, and the source of the cells is not necessarily the most important.

Another interesting observation is the fact that only 16 trials (36%) could be definitely categorised as testing stem cells (i.e. cells that are generally accepted in the scientific community as being pluripotent), which rises to 24 (55%) if trials using MSCs (generally thought to be multipotent) are included. There were marked differences in the way that interviewees described their cells, and in particular the extent to which they associated their treatment with the term 'stem cell'. Some were very specific that the treatment was a stem cell treatment; for instance, when asked about the type of treatment, Interviewee 3 said: *"yes, a stem cell transplant."* Others, however, were keen to distance themselves from the term:

> "There are so many different types of, you know you've got the embryo all the way through to the adult. So we focus on adult cells

> - I particularly only think of adult cells, and I don't tend to use the word stem cells very often." (INT15)

This quote suggests that the reluctance to use the term stem cell was partly just an attempt to be precise and scientifically accurate, but there was also evidence that some interviewees felt that the term also raised certain expectations. For instance, Interviewee 15 explained how the term is perceived in his clinical area:

> "I think the interpretation of the word stem would be an optimism, and great hope that that would be a very new exciting sort of treatment which would repair their body extremely effectively." (INT15)

These expectations were viewed as problematic by many, for instance Interviewee 10 raised the concern that they are unlikely to be realistic in his clinical area:

> "I do worry that stem cells are kind of promoted literally as miracles, you know - it ain't gonna be like that." (INT10)

Clearly, then, the use of the term stem cell to describe a treatment is not a neutral one, particularly in terms of patient expectations, and this is a theme that we will return to in Chapter 4.

Along with the cell source and potency, another important distinction between therapies is the extent to which the cell population is selected or purified (i.e. cells are isolated based on some pre-determined criteria, such as plastic adherence for MSCs, or expression of a particular gene). Those in favour of using a mixed population suggest that there may be benefits to having a variety of cells working together. For instance, the SIAMMS-II trial protocol specifies that a non-purified population of cells was used in the expectation that all the cell subpopulations would work together (Rice et al., 2015). This is not necessarily a consensus view, however, as Interviewee 1 explained:

> "You can identify certain antigens in melanoma, for example, which T-cells react against. And if you select those cells and use those alone they're actually less effective than if you don't select them. … So the initial stage was impure population which sort of worked,

> but people thought, well if we get a pure population it will work better. But actually, it didn't - it worked less well." (INT1)

A clinical scientist speaking at a conference also expressed this view, and pointed out that mixed cell populations showing greater efficacy is unsurprising from a biological perspective, as cells are used to being next to each other and communicating. He also argued that using mixed populations is logistically advantageous, as it makes the cell product easier to produce because there is no need to characterise the cells (Field notes 21/11/13).

In contrast to these benefits of using a mixed population of cells, a number of potential drawbacks were also highlighted during my fieldwork. The same scientist who highlighted the logistical benefits of using a mixed population also raised the concern that this may become problematic in the future, because regulators will probably begin to ask for more detail about the exact characteristics of the cell population. A number of interviewees also noted that using a more homogenous cell population makes it easier to understand the effect of the cells. For instance, Interviewee 4 reflected that:

> "It was an important decision though, and again I took advice, and the advice was very strongly to do an unselected procedure. And I'm not sure I'd do that now - you might learn more from a bit more selection." (INT4)

Clearly, then, the decision about whether to purify the cells used in a clinical trial involves a trade-off between likely efficacy, logistical considerations, expectations of future regulatory requirements and the precision of the evidence generated. Because there is no consensus yet about the best approach, these trade-offs appear to be being made on a trial by trial basis. This leads to fragmentation in the field, even amongst trials of very similar therapies, such as the Oswestry ACI method - which does not pre-specify the exact type and number of cells - and other forms of ACI, such as ChondroCelect, which do (NICE, 2015). This is further complicated by the fact that very few trial protocols explain the cell manufacturing process in detail, making it difficult to know exactly what cell population was used. These complexities and

uncertainties have significant implications for innovation in the cell therapies, which Chapter 6 will examine in more detail.

Mode of delivery

As highlighted by Foley and Whitaker (2012), mode of delivery is an important factor in the practicality of a cell therapy. Following Foley and Whitaker's model of classification, Table 3.5 details the breakdown of 'products' and 'procedures' being tested in UK cell therapy trials, showing a relatively even split between the two amongst both clinician and company-led trials. This contrasts with Foley and Whitaker's findings, which suggest that only 30% of global trials use cells as products. The difference appears to be largely driven by the higher proportion of clinician-led trials in the UK that use products (57% in comparison to 27% reported by Foley and Whitaker). This may be due to a perception amongst UK clinicians that simplifying the procedures for delivering the cells is beneficial. For instance, one clinician involved in an early tissue engineering trial explained that the simpler a device or product is, the easier it is to get through regulators and minimise variability and risk (Field notes 01/05/14). Even when cell delivery does involve a surgical procedure, there is a drive to reduce complexity. For instance, one surgeon was keen to trial techniques which would allow him to inject the cells into the patient rather than using a membrane (Field notes 21/05/15), and Interviewee 5 explicitly emphasised the simplicity of the mode of delivery for his treatment, despite it being a surgical procedure.

Table 3.5: Mode of delivery broken down by type of trial

Mode of delivery	Industry-led		Clinician-led		TOTAL	
	No.	%	No.	%	No.	%
Product	7	58%	18	56%	25	57%
Procedure	5	42%	14	44%	19	43%
TOTAL	**12**	**100%**	**32**	**100%**	**44**	**100%**

Alongside the issue of cell *delivery*, it is important to recognise that many cell therapies involve complicated procedures for cell *harvesting*, even if the resulting treatment can be administered as a product. 18 of the 25 UK trials categorised as products required relatively complex procedures for harvesting the cells. The majority of these are autologous treatments, in particular immunotherapies that require leukapheresis for harvesting peripheral blood cells. Although this is a routine procedure, it still adds complexity and cost to the trial, as Interviewee 5 pointed out:

> "Who wants to be connected to a centrifuge - number 1, and it's expensive - number 2, and it takes quite a bit of staff time." (INT5)

Cell harvesting procedures can also introduce regulatory complexity, because the framework developed for these processes did not necessarily have cell therapies in mind, as Interviewee 12 explained:

> "Now here comes your problem – the only sites that are licensed under the blood directive are National Blood Transfusion centres. So the MHRA says you've just got to get blood transfusion centres to do it, but they take blood from normal healthy donors - they don't take blood from patients. If you're going to put a needle in a patient you've got to be CQC'd, so that's a hospital. So you can't, through a regulatory cock up you've effectively made a trial completely impossible in this country." (INT12)

This additional complexity is introduced because autologous cell therapies are distinctive in that they involve both surgical procedures and the manufacture of a medicine, as Interviewee 12 went on to explain:

> "Because many many many of these products require material from the patient - so it's the only pharmaceutical in the world where the patient and the hospital is involved in manufacturing the drug." (INT12)

Allogeneic treatments are often perceived to be a more viable option for commercial development, in part because they often involve a simpler mode of cell harvesting and delivery. This is certainly the case for some of the allogeneic treatments being trialled in the UK - for instance, the MultiStem product being trialled by Athersys and the CTX line being trialled by ReNeuron both use established cell lines that can be delivered to the hospital, and thus do not require specific harvesting or manufacture for individual patients. However, some allogeneic treatments still require cell harvesting, either for individual patients or to treat a small number of patients. Sometimes this can be undertaken as part of an existing surgical procedure, and in these cases the harvesting is generally relatively straightforward and does not add significant complexity to the trial. For instance, Interviewee 6 explained that she received cells from a department undertaking bone marrow transplants, which she then expanded in her lab to treat multiple patients from one donor:

> "The marrow is being procured at [hospital name] in their theatres with proper consent. They'll take the first pull of marrow - remember they're collecting a big bag for the transplant - they'll take the first pull, which is a couple of mls, for manufacturing MSCs, and send them to us." (INT6)

However, in other cases the procurement of allogeneic cells requires additional procedures which add complexity to a trial. For instance, Interviewee 2 explained that harvesting of cells from aborted foetuses is not considered a viable option in the long term, due to limited availability and the need to coordinate three sources to treat one patient. Harvesting allogeneic cells also creates additional complexity because of the involvement of an additional regulator, the Human Tissue Authority (HTA), creating problems that will be discussed in more detail in Chapter 7. Thus, although the UK has a higher proportion of trials being delivered as products, it appears that this does not always mean that these are less invasive treatments, or less complex from a regulatory and logistical perspective.

Mode of action

Table 3.6 details the presumed mode of action of the treatments being tested in UK cell therapy trials, following the code frame used by Li et al. (2014). It shows that the largest group is immunotherapies, and only a third of trials are testing regenerative treatments. This differs markedly from the global picture reported by Li et al., who found that the vast majority of cell trials were regenerative, and only a very small proportion were immunotherapies. Again, this difference is partly due to their methodology excluding adoptive T-cell trials, which make up a significant proportion of UK immunotherapy trials. It may also be partly due to their use of the term 'stem cell' in their search strategy, which may have been more likely to return trials with a regenerative aim. These methodological differences make it difficult to judge the extent to which the UK differs from the global picture in terms of the types of cell therapies being developed, but it is possible that the availability of HE in the UK means that fewer regenerative treatments are tested in clinical trials.

Table 3.6: Presumed mode of action

Mode of action	**No.**	**%**
Regeneration (goal of the CT or the SC mobilization is to regenerate tissue)	14	32%
Cell Therapy (cell therapy for purposes other than regeneration, e.g. immunomodulation)	11	25%
Immunotherapy (using or modifying the immune system to target infections or cancer cells)	19	43%
TOTAL	**44**	**100%**

These results indicate that rather than being largely synonymous with regenerative medicine, cell therapy trials in the UK are actually quite evenly split between those that aim to regenerate tissue, those that aim to utilise or boost the immune system, and those that use cells as therapeutic agents. Rather than a homogenous group, therefore, these trials should perhaps be considered as three separate categories, which share some characteristics but also have important

differences between them. This fragmentation is reflected in the way interviewees described the therapies they were developing, which reflects the distancing from the terms 'stem cell' and 'regenerative medicine' discussed earlier in this chapter. Many interviewees distinguished their work from regenerative medicine by specifically using other terms to describe it, for instance Interviewee 9 described the therapy as *"cellular therapy and immunotherapy"*. Some went even further than this and explicitly rejected the term regeneration, for instance Interviewee 4 said: *"no I don't want to use the word regeneration - they're re-seeding of the bone marrow."* Another interviewee explained in detail why he felt the term regeneration did not apply to the cell therapy he was developing:

> "We don't believe they're regenerative in nature - we're not regenerating [cell type] that have been damaged from the [disease]. The cells may have properties to help a person mobilise their own endogenous stem cells, but we think the cells go in basically and kind of quiet or call time out on the immune, hyper-immune and hyper-inflammatory response that happens after [acute clinical event]." (INT11)

Clearly, then, not all cell therapy trialists relate to the concept of regeneration overall, but rather they have more specific, technically-precise understandings of how the treatments work.

Another dimension to take into account when looking at the types of therapies being developed in the UK, whether regenerative or not, is the extent to which they offer the potential to 'cure' a patient, rather than simply providing incremental benefits over and above existing treatments. Much of the hype about stem cell treatments and regenerative medicines suggests that they have the potential to cure debilitating diseases such as diabetes, multiple sclerosis and Alzheimer's disease, offering a revolutionary alternative to currently available drug treatments. Many interviewees, however, were much more circumspect in their expectations. For instance, Interviewee 7 described the cell therapy he was developing as more akin to the best available drug, but without the side effects:

> "Cell based therapies around [cell type] will never cure anyone of [disease] … the best response you're going to get with a [cell type] is the best response you'll get with a drug." (INT7)

These findings suggest that there is a significant disconnect between popular understandings of regenerative medicine and the majority of treatments that are actually being trialled in the clinic.

As well as highlighting this disconnect between expectations and reality, my fieldwork also suggested that it could cause problems for cell therapies. For instance, in a discussion at a cell therapy network conference, one clinician said that he felt a particular tissue engineered product was perceived negatively from a reimbursement point of view because it had only been demonstrated to work for a few years, rather than providing a permanent cure as might be expected from a 'regenerative' therapy. He felt that the results were in fact more positive than they were perceived to be, because the patient at least had a few more years at a higher quality of life than they would have had otherwise (Field notes 21/11/13). The link between treatment effect and cost effectiveness was also mentioned in the interviews, for instance Interviewee 9 explained that the high up-front cost of the cell treatment meant that it would need to achieve dramatic results in order to be worth pursuing: *"if it was just a miracle cure then I suppose yes, we would put the effort into it."* Expectations, particularly in terms of longevity and the significance of the treatment effect, thus clearly have an impact on the development of a cell therapy, and this will be explored further in Chapter 7.

3.3.2 Characteristics of cell therapy trials

Trial phase and outcomes

Table 3.7 (overleaf) details the breakdown of UK cell therapy trials by phase and primary outcome measure, which are indications of how far the trialling has advanced. The majority of trials are early-phase, with over half at either Phase 1 or transitional Phase 1/2, and there are only two treatments have advanced as far as Phase 3 trials. Both of these trials - ASTIC (Crohn's disease) and BAMI (acute myocardial infarction) - involve using HSCs as a therapeutic, as opposed to regenerative, treatment.

Table 3.7: Trial phase and primary outcome measure

Phase	Efficacy		Safety		Safety and Efficacy		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Phase 1	1	6%	7	39%	4	44%	12	27%
Phase 1/2	3	18%	7	39%	4	44%	14	32%
Phase 2	11	65%	4	22%	1	11%	16	36%
Phase 3	2	12%	0	0%	0	0%	2	5%
TOTAL	**17**	**100%**	**18**	**100%**	**9**	**100%**	**44**	**100%**

Despite being described as Phase 3 on the trials registry, ASTIC is a small trial that only aimed to recruit 48 patients, and was in fact halted after only 37 patients were treated due to safety concerns (related to the chemotherapy used alongside the cell treatment, rather than the cell therapy itself). BAMI is still recruiting, aiming to recruit 3000 patients in total across all sites and countries, and is therefore the only large and ongoing Phase 3 trial of a cell therapy in the UK. These findings indicate that the cell therapies being trialled in the UK, particularly those that could be considered regenerative in nature, are at a very early stage of development. It is likely that, like the majority of early-phase drug trials, many of these treatments will fail to show a significant treatment effect in later confirmatory trials. Interviewee 5 highlighted this issue by comparing the situation to other early-phase cancer trials:

> "[Name of cancer trials manager] will tell you, a new agent in a Phase 1 - if you get a 10% response rate that's probably as good as it gets." (INT5)

Even those trials that do show promising results will face additional challenges in later-phase trials, because the amount of validation increases and by Phase 3 they will need to be fully GMP-compliant (Field notes 23/09/15 and 01/10/13).

To some extent, this analysis presents a relatively pessimistic assessment of the short and medium-term prospects for cell therapies in the UK. However, the data also highlights an interesting distinction between cell therapy trials and traditional drug trials, which may have implications for this pessimistic assessment. Although many of the trials have safety as a primary outcome, many are also testing for efficacy, even some of the Phase 1 trials which might be expected to be testing safety alone. Moreover, even those trials that do not state efficacy as a primary outcome are often monitoring it as a secondary or exploratory measure, as explained by Interviewee 17:

> "It's primarily a safety outcome. But having said that the patients will get a, you know, an efficacy outcome - but we're not measuring that as part of our trial, which is semantics really." (INT17)

This suggests that although the majority of cell therapy trials are not very advanced on paper, in reality they are generating evidence that in drug trials might not be possible until much later in the trialling process.

Testing for efficacy in early-phase cell therapy trials is possible because every one of these trials is being conducted with patients, unlike Phase 1 drug trials, which are traditionally conducted with healthy volunteers. This suggests that the trajectory for cell therapy trials may not completely adhere to the model used for drugs, a view that is supported by data from the interviews. Interviewee 17 explained that the traditional terminology for trials didn't fit with how he perceived the process for his treatment:

> "I think even just the way of calling things Phase 1, 2, 3 and 4 is really redundant ... our study is called Phase 1, because it's primarily a safety outcome … and then we'll do a Phase 2, which will be our registration trial ... But again, that's just a, you can take out the phase kind of nomenclature and just call it a registration trial or a clinical trial. But it will only be 50 patients probably." (INT17)

This pragmatism about the number of patients likely to be recruited underpinned many interviewees' expectations that the treatment would never reach Phase 3. This

was sometimes due to the rareness of the condition being treated (as was the case for Interviewee 17), but even for prevalent conditions it was sometimes felt that the treatment was too experimental and too invasive to be tested in large numbers of patients:

> "One of the problems with these types of trials - especially for invasive therapy where you're sticking things in people's brains - you may say, well in order to get an effect you know you need 80 patients - well you can't do that. So to some extent you're hampered by pragmatic considerations." (INT7)

The fact that it may not be practical for many cell therapies to be tested in large Phase 3 trials means that despite their small numbers, the supposedly 'early-phase' trials in my dataset may in fact be 'late-phase', in that they will not lead to further, larger trials.

Another way in which cell therapy trials appear to depart from the traditional phase model for trials is the testing of dose. Early-phase drug trials, particularly Phase 1 or Phase 1/2, are traditionally used to test different doses of a drug in order to establish safety and toxicity levels (so called 'dose-escalating' trials). However, only 12 (27%) of trials in the dataset tested different doses of cells, which is perhaps a lower proportion than might be expected, given the high number of early-phase trials. Some interviewees suggested that, in contrast to drugs, dose response does not appear to be relevant to the toxicity or efficacy of cell therapies. For instance, Interviewee 1 explained that:

> "We don't worry too much about things like number - that's just based on the experience that it doesn't matter that much." (INT1)

In contrast, other interviewees were keen to follow the 'best practice' pathway established by drug trials, but they experienced difficulties using traditional dose-escalating methods for cellular treatments:

> "The general aim of any first-in-man clinical trial is going to be about safety really. Determining the safety of your new agent and determining the recommended dose of that agent for Phase 2

> testing. So those really are the two primary goals of our trial … and again that is a very difficult issue when it comes to a cell therapy, unlike a small molecule or an antibody etc. But we are dose escalating." (INT5)

It seems, then, that there are both clinical and practical reasons for the lack of dose escalation in many early-phase cell therapy trials.

Two main issues were raised about using specified doses of cell therapies. Firstly, it is often not possible to predict in advance the number of cells that will grow in the lab, particularly for autologous therapies. This creates difficulties if a particular dose is required for treatment, as explained by Interviewee 12:

> "What you get out is only very very marginally affected by what you do to it. It's mainly affected by what you put in … you can't say that the process will always deliver the same product, because you're starting with different materials." (INT12)

This uncertainty creates an additional tension in the delicate balance between research and care, and Chapter 4 will explore the various ways that trialists attempt to reconcile these competing priorities. The second concern raised in the interviews is the fact that for many treatments the cells will proliferate *in vivo* at a rate that varies considerably between patients, meaning that the dose that is administered is not a good indication of the dose that the patient is actually exposed to, as explained by Interviewee 12:

> "The thing about lymphocytes is that they proliferate *in vivo* in response to an antigen, so the dose you give isn't the dose that's effective. Now no other drug in the world, in the history of drugs, pharmacology, has done that. There's never increased dose after you've given it to the patient." (INT12)

Clearly this creates significant uncertainty about the clinical effect of cell therapies, an issue that will be examined further in Chapter 6.

For a variety of reasons, then, it appears that the traditional phase model of clinical trials is unlikely to be relevant or practical for many cell therapies. This appears

to be particularly the case for tailored autologous therapies, and for those therapies that are complex to deliver. Interviewee 9 actually drew this distinction directly:

> "The other question is, is Phase 1, 2, 3, 4 equally applicable to cell therapies? Because actually most of these studies are small numbers of patients - are you ever going to be able to do a sort of 300 patients Phase 3 trial of a cellular therapy? I guess you could if they're off the shelf and they're easy to administer, but the sorts of things we do, they're bespoke therapies. I don't think we could ever do a Phase 3 trial." (INT9)

He went on to suggest that, from a trials perspective, tissue engineered products have more in common with surgical procedures than drugs:

> "Many of these tissue engineered products probably won't ever get to a Phase 3 trial … they are effectively trials of surgical procedures, and those have never gone through a Phase 1, Phase 2, Phase 3 process." (INT12)

It appears, then, that some cell therapies may require a different approach to the usual clinical trials pathway, perhaps one more akin to the testing of surgical procedures. This raises important questions about how evidence is generated (which will be explored further in Chapter 7), uncertainty and risk (to be discussed in Chapter 6), and patient agency and the therapeutic misconception (which will be addressed in Chapter 5).

Trial methods

Alongside the phase and aims of cell therapy trials discussed above, the methodological characteristics of these trials (detailed in Table 3.8, overleaf) provide further insight into the challenges cell therapy trials present for the traditional trials model.

Table 3.8: Methodological characteristics broken down by phase

Phase	Randomised		Blinded	
	No.	%	No.	%
Phase 1	3	25%	0	0%
Phase 1/2	2	14%	2	14%
Phase 2	10	63%	8	50%
Phase 3	2	100%	0	0%
TOTAL	**17**	**39%**	**10**	**23%**

Perhaps the most important thing to note from this data is that only 17 (39%) trials have a randomised control group, which could reduce the perceived validity of these trials. Although the sociological literature (discussed in Chapter 7) suggests that some clinicians might be opposed to randomisation on ethical grounds, this does not appear to be the case here, as none of the interviewees working on uncontrolled trials raised any objections to randomisation in principle. Rather, it appears to be a product of the early stage of many of the trials, with the uncontrolled trials being predominantly those at Phase 1 or 1/2. Although this is not unexpected, as Phase 1 drug trials would also typically be uncontrolled, the fact that Phase 3 trials might not be possible for cell therapies increases the reliance on data from early trials. The lack of randomisation in these trials could thus potentially present an obstacle to the eventual approval and/or reimbursement of these treatments, unlike drugs, where randomised data will be generated later in the trials process.

Even those trials that do have randomised control groups are not necessarily double-blind, which is considered the 'gold standard' for RCTs. The majority (77%) are open-label, which reflects the difficulty of blinding in surgical trials. In many cases blinding would simply not be possible - for instance, in the case of the tissue engineered trachea there is no other treatment or device that could be plausibly be considered as a placebo, and no way to mask the fact that the treatment has been given. However, in cases where cells are injected then blinding is often possible, for

instance Interviewee 6 (who produced cells that were then sent out to the clinical sites participating in a trial) described the process as relatively straightforward:

> "I'm the only one who knows that I'm giving them a placebo - the doctors and the patient don't know." (INT6)

In cases where more complex surgery is required to deliver the therapy, 'sham' surgery is often an option for maintaining blinding, however, none of the trials in the dataset appear have used this method. This may be because some surgeons have ethical concerns about conducting an invasive procedure that does not provide any clinical benefit, as explained by Interviewee 7:

> "The problem with sham surgery as we saw it is that one, was it necessary, which is a separate question in itself, secondly it's putting the patients through quite a lot, so they have to have a little hole drilled through their skull, they have to be put on immunotherapy in order to control for that so that carries with it a risk … and the other issue is, you know, is it a good use of medical health resources to block a theatre for three or four hours and bring someone into hospital for a day or two who is actually having no procedure?" (INT7)

It seems, then, that although blinding should be possible for many cell therapies, it is likely to be problematic for many tissue engineered products, and/or those that involve complex or invasive surgical procedures.

Other than randomisation and blinding, sample size is perhaps the most important factor that affects the perceived validity of a trial. Table 3.9 (overleaf) details the sample size of the trials in the dataset, showing that most are relatively small, with only six (13%) expecting to recruit more than 100 patients.

Table 3.9: Sample size broken down by number of trial arms

Sample size	One arm		Two arms		Three arms		Four arms		TOTAL	
	No.	%	No.	%	No.	%	No.	%	No	%
≤ 10	9	38%		0%	0	0%	0	0%	9	20%
11-50	14	58%	10	67%	0	0%	0	0%	24	55%
51-100	1	4%	3	20%	1	25%	0	0%	5	11%
101-1000	0	0%	1	7%	3	75%	1	100%	5	11%
≥ 1001	0	0%	1	7%	0	0%	0	0%	1	2%
TOTAL	**24**	**100%**	**15**	**100%**	**4**	**100%**	**1**	**100%**	**44**	**100%**

This data also indicates that the majority of trials only have one or two treatment arms, suggesting the majority are using a very traditional trial design. Indeed, from the information gleaned from online registries and protocols, it appears that none are using complex, innovative or non-standard methods, and notably none are using adaptive statistical methods, such as sample size re-estimation or 'drop the loser' designs. This may be partly due to a lack of awareness on the part of the individuals designing the trials, as many of my interviewees had no or very little knowledge of adaptive statistical designs. However, even those interviewees who were familiar with adaptive methods felt that they would be problematic for cell therapy trials. For instance, Interviewee 17 explained that they had considered adaptive methods for their Phase 1 study, but had been put off by the need for existing data on likely outcomes, the need to specify in advance what might be changed, the need to have outcome data accumulating whilst the trial was still recruiting, and the risk of reducing the power of the trial by splitting an already small sample into sub-groups.

Interestingly, although there was little evidence of cell therapy trials adopting advanced or innovative statistical methods, three trials (7%) used a cross-over design, meaning that all of the participants received the active treatment at some point during the trial. Cross-over designs are only possible for treatments that do not need to be administered immediately, and as such would only have been appropriate for a

subset of trials, so it is interesting that there are three instances of this design being used. The rationale for cross-over trials is often an ethical one, as explained by Interviewee 3:

> "You've got a group of patients for whom no treatment is really working for them, therefore you can't say 'well you can't have the treatment and you can.' So treatment was offered to everyone, it was either early transplant or delayed." (INT3).

It seems, then, that the cross-over method could allow some cell therapy trialists to overcome the tension between research and care that many clinicians involved in trials experience (discussed further in Chapter 4). The design also offers some benefits in terms of the evidence generated, as highlighted by Interviewee 4:

> "Some people think that's a slightly unorthodox approach. I think that on the whole it's yielded, and is yielding, more information than would otherwise be the case." (INT4)

This suggests that cross-over designs allow trialists to generate useful information for the continued development of a therapy, as well as the more formal evidence required by regulators - a theme that I will return to in Chapter 6. Is also interesting here that Interviewee 4 mentions that the cross-over design was perceived as unorthodox in some circles, given that this is a relatively well-established method. This is just one of many examples of how unfamiliar the world of trial methodology is to many cell therapy trialists, a theme which I will expand on in Chapters 4 and 5.

3.4 Discussion

The most striking aspect of the UK cell therapy trials landscape described in this chapter is its fragmentation. Trials activity is split between immunotherapies, cellular therapies and regenerative medicines (which account for only a third of all trials), and there are marked differences between trials in terms of the procedures used to harvest and deliver the cells. The interview data indicates a range of differing perspectives on key aspects of cell therapy development, including the value of purified cell populations, the relevance of dose, the practicality of blinding, and the

appropriateness of Phase 3 trials. It appears, then, that to treat cell therapy trials as a homogenous category is to misunderstand the actual characteristics of the field. In fact, it seems that there is no such thing as a 'typical' cell therapy trial - an issue that Interviewee 15 raised explicitly:

> "If you say cell therapy to some people it's all about scalability and manufacturing of large volumes of millions of cells, and if you say it to me I'm thinking of a bespoke, expensive, minimally manipulated cell product near the patient … So this is a cell trial, meaning that there's a cell involved, but it really doesn't help you understand what we're doing." (INT15)

This heterogeneity is an important factor to consider when analysing the field, because the specific characteristics of a cell therapy have considerable implications in terms of (amongst other things) the logistics of cell manufacturing, expected treatment effect, availability of funding, patient expectations, appropriate outcome measures, and reimbursement.

My findings also suggest that some of the terminology and classifications used in analyses of the field might not be as useful as is sometimes assumed. For instance, it is clearly not valid to use the terms 'regenerative medicine' and 'cell therapy' interchangeably: regenerative medicine accounts for only a subset of cell therapy trials, and many cell therapy trialists actively distance themselves from the term. Likewise, the term 'stem cell' is highly problematic scientifically, and is either actively rejected or deemed of limited relevance by many trialists of cell therapies. Despite this, recent policy initiatives aiming to address obstacles to innovation in cell therapies have largely done so under the banner of regenerative medicine, and the term stem cell is frequently used in both policy literature and the media to describe such treatments. To some extent this is merely a reflection of the messiness of the early stages of innovation, before clear, settled boundaries have been drawn. However, it is also important to recognise that the use of terms such as regenerative medicine or stem cell is not neutral, but creates expectations of a therapy that is both extremely innovative and highly effective.

Another element of cell therapy terminology that is called into question by my findings is the dichotomy between allogeneic and autologous treatments. Despite often being used in both policy and academic literature as a natural segmentation of cell therapies (see for instance Foley and Whitaker, 2012), the provenance of the cells does not in fact appear to be a good predictor of the difficulty of undertaking a cell therapy trial. Instead, this is more likely to be determined by the potency of the cells and the amount of manipulation involved, and/or the complexity and risk of the procedures for harvesting and delivering them. The distinction between autologous and allogeneic is likely to become even less relevant if the use of IPSCs becomes more prevalent, because although technically autologous, these cells are both pluripotent and highly manipulated, and thus more likely to fit the model of allogeneic cells in some regards. The product/procedure and company/clinician distinctions often used in the literature also appear to be problematic - for instance, a simple procedure for delivery of the cells doesn't necessarily mean the cell harvesting is straightforward, and companies are often involved in the development of treatments which require complex clinical procedures, whereas clinicians are leading some of the more straightforward 'cells-as-drugs' trials. It is also notable that a significant minority of current trials are taking place in clinical areas that are considered particularly challenging for regenerative medicine, and the clinical areas with the highest trials activity do not align with the products that have been licensed so far. All of these observations suggest that there are many complex and interlinked factors determining the successful translation of cell therapies, and that to understand the obstacles facing a particular trial we must look beyond the classifications traditionally used to segment the field.

The fragmented nature of cell therapy trials is also reflected in a number of tensions within the policy framework and clinical research environment. Notably, the majority of trialists align themselves more with their clinical area than with 'regenerative medicine' or 'cell therapies', suggesting that cell therapy trialling is not yet, and indeed may never be, a cohesive field. This raises the issue that policy initiatives such as the Cell and Gene Therapy Catapult, or the mock HTA appraisal conducted in response to the House of Lords report in 2013, are likely to be relevant

to only a subset of cell therapy trials. Furthermore, there appears to be a disconnect between the regulatory and policy framework, which largely assumes a commercial development model, and the current activity taking place in the clinic, where most trials are publicly-funded and investigator-led. Cuende et al. (2014) note that one of the limitations of the ATMP legislation is that it doesn't work very well for treatments that are minimally manipulated and don't have a commercial interest. Given that this appears to be where the majority of trialling is currently taking place, this may place significant limitations on the future development of the field.

The UK policy environment could, in principle, be adapted to better reflect the realities of the trials taking place in this country. The regulatory environment, however, is largely dictated by EU legislation, and until very recently this meant that any changes would have to come at a European level (Hitchcock, 2013). This situation has potentially changed, however, in the light of the 2016 referendum result,[8] because if the UK leaves the EU it could, in theory, change the legislation governing both cell therapies and clinical trials. The EU Clinical Trials Directive has already been transposed into UK law, so there will be no immediate effect on the general regulations governing clinical trials, however there is now the possibility of the UK unilaterally changing these regulations in the future. The ATMP regulations will need to be adopted into UK legislation, and could theoretically be changed completely, as could the requirements for marketing authorisation, which are currently dictated by the EMA.

Although leaving the EU presents an opportunity to address some of the limitations of the current framework, my findings suggest that the UK adopting a differential approach to cell therapy trials could be problematic, not least because the lack of harmonisation between member states already creates significant challenges for trialists. Adopting a different regulatory framework to the EU might also only have limited benefits, because very few interviewees described

[8] Note that my fieldwork was conducted before the referendum, at a time when continued UK membership of the EU was assumed.

experiencing challenges that were specifically caused by European legislation. The European regulatory framework could perhaps therefore be considered an *ultimate* cause of the 'challenge' of cell therapy trials, in that it means that most cell therapies now have to go through a much more exacting trials process than previously, but the specific issues that this creates, i.e. the *proximate* causes, are predominantly local in nature, and could therefore (in principle) have local solutions. The remainder of this thesis will explore these challenges in depth, and from a variety of perspectives, beginning in the next chapter with a detailed exploration of the social dynamics of cell therapy trialling.

4. Clinicians, companies and patients: the social world of the RCT

As I discussed in Chapter 1, the sociological literature suggests that trials involve the construction of new and changeable dynamics between three key actors involved in clinical research: clinicians, companies and patients. With its focus on the perspectives and actions of different actors within the field, this provides a useful framework for examining the social dynamics of UK cell therapy trials, and for exploring the contingencies and provisionality that these dynamics create. I begin this chapter with a brief overview of the key literature concerning these social dynamics, setting out the framework which is then used in the rest of the chapter as the basis for examining the role of each of these actors in trials of cell therapies.

4.1 A sociological understanding of clinical trials

Clinical trials can be sponsored and/or funded by a range of organisations, including universities, NHS Trusts, research councils, charities, philanthropists and commercial organisations. Regardless of who sponsors or funds a trial, however, the research itself generally takes place in a clinical setting, with clinical staff undertaking the day-to-day tasks involved in recruiting patients, administering the treatment and collecting data.[9] The conduct of a trial therefore creates two distinct relationships in the clinic: that of clinician-patient and that of researcher-subject. The clinician is thereby acting as both caregiver and researcher, and to some extent these two roles can appear incompatible, because the objectives and requirements of providing treatment differ significantly from those of conducting research (Lidz et al., 2004; Easter, 2006). A number of studies have shown that doctors experience trials as a challenge to their core task of providing care (Taylor, 1992; Mueller, 1997). For

[9] Clinical staff would include doctors, research nurses or other clinically trained staff such as physiotherapists or clinical psychologists. Even those trials which take place in dedicated facilities outside of the NHS, such as CROs or clinical research units, would normally use clinical staff for the treatment of patients/participants.

instance, treatment protocols for trials are developed with the needs of the research in mind and rarely take the impact on the patient into account, whereas an individual clinician would normally consider a patient's specific circumstances when considering different treatment options (Mueller, 1997).

One area that presents a particular challenge to the clinician's core role is the tension between collective and individual equipoise. Collective equipoise requires there to be uncertainty as to the most effective treatment at a *communal* level - i.e. the clinical community as a whole must be in equipoise. Individual equipoise, on the other hand, requires a specific physician to be uncertain about the relative benefits of one treatment over another. Collective equipoise provides the ethical justification for random allocation of treatment, and is required for a trial to gain approval, but during the trial itself individual equipoise comes into play in the relationship between the patient and clinician (Chard and Lilford, 1998; Robinson et al., 2004). Collective and individual equipoise could be in conflict for any number of reasons; for instance, an individual clinician, in consultation with their patient, may believe that one of the trial arms would be more beneficial than the other. Randomisation, in these circumstances, fundamentally challenges clinical autonomy and the traditional dynamics of physician-patient relationships. This presents an ethical dilemma for any clinician faced with a conflict between their responsibility of care to their individual patient and the requirements of a research project, which may or may not benefit many patients in the future (Mueller, 1997).

The conflict between research and care means that clinical staff might not always adhere to, and could in fact deliberately subvert, aspects of the research that they feel conflict with their ethical responsibilities as a caregiver. There are examples of clinical staff going to extreme lengths to ensure patients are allocated to the group they perceive to be most appropriate, for instance steaming open sealed randomisation envelopes, breaking into locked offices and filing cabinets, or keeping a record of treatment allocations in an attempt to 'break' the sequence code and predict future allocations (Hewitt et al., 2009). There have also been examples of clinical staff deliberately breaking treatment protocols after randomisation because they felt strongly that one of the treatment arms was more effective, and that it was

therefore unethical to withhold this treatment from any patient. In one of the most famous examples, nurses conducting a trial testing the provision of oxygen to premature babies were found to have given oxygen to the control group at night because they were so convinced that it was lifesaving (Torgerson and Torgerson, 2008). The health services research literature refers to such activity as 'subversion', presenting it as both aberrant and irrational, and increasingly strict control measures are used to reduce its prevalence. In a sociological context, however, these incidents can be seen as clinician-researchers attempting to reconcile the conflict inherent in their dual role, by manipulating the 'research' of the trial to better align with the demands of 'care'.

Another way in which clinicians address this conflict is by adapting the way that they conceptualise 'care' in order to accommodate and/or compensate for the drawbacks of 'research'. One of the earliest qualitative studies of clinical trials highlighted the ways in which clinical staff adapted their relationships with patients, moving from an authoritative 'physician-patient' model to treating trial participants as 'pseudo-colleagues', and giving them the 'red carpet' treatment (Mueller, 1997). Another interesting study showed that different types of clinical staff have different ways of reconciling the conflicts of research and care: physicians conceived of the participants as research subjects, whereas nurses conceived of them as patient-volunteers in need of treatment, and the balance between these two perceptions was constantly in flux during the conduct of the trial (Mueller, 1997). Participation in clinical trials thus clearly challenges the traditional role of clinicians as caregivers, which they address in a variety of ways, from adjusting their expectations of the relationship with patients to obstruction and sabotage of the trial process.

In addition to challenging the role of clinicians as caregivers, trials also create another similar tension because of the dual role played by participants, who are both patients and research subjects. The recruitment of patients is a crucial and often problematic aspect of any clinical trial, particularly Phase 3 trials that need large samples to achieve statistical power. Policy initiatives often seek to facilitate recruitment by framing trial participation as a "scarce social good that needs to be distributed equitably" (Timmermans, 2010). This position can often be valid in a

medical context, particularly when alternative treatment options are limited, but it fails to reflect the complex medical and social realities of patient involvement in trials. Until the middle of the last century, it was not unusual for clinical research to take place without the knowledge or consent of the participants. This led to a number of high-profile ethical controversies, and the eventual development of a stringent ethical framework protecting the rights of patients involved in clinical research. Central to this framework is the concept of informed consent: i.e. that a patient must not only give their consent to taking part in an experiment, but that in order for that consent to be meaningful they must fully understand what they are consenting to.

Despite the introduction of rigorous informed consent processes, a number of studies have shown that participants still frequently overestimate the benefits and underestimate the risks of participating in medical research (Lidz et al., 2004). Crucially, many participants do not understand the difference between research participation and medical treatment, and therefore tend to overestimate the likelihood that the trial will directly benefit them medically, a phenomenon known as the therapeutic misconception (Easter, 2006). One of the features of RCTs that participants have most trouble reconciling is the process of random allocation. One study found that although trial participants recalled that some element of chance had been involved in the allocation of their treatment, they had difficulty believing that this was really how their treatment was allocated, feeling that it was too 'haphazard', and at odds with the amount of information they had been asked to provide about their condition (Featherstone and Donovan, 2002). Another study showed that participants struggled to accept that individual clinicians could truly be unsure about which treatment was more effective, and didn't feel it was acceptable for a clinician to decide on their treatment purely at random (Robinson et al., 2004).

The difficulties that patients have in making sense of their participation in clinical trials mirror those of clinicians, further highlighting the ways in which trials challenge traditional concepts of care, and fundamentally alter the relationship between clinician and patient. In this context, presenting trial participation as a 'scarce social good' may undermine informed consent by exacerbating existing misconceptions. This is particularly pertinent to early trials of experimental

treatments, which are solely designed to test toxicity and are therefore not even intended to provide any significant medical benefit to participants. Despite these concerns, however, there is also evidence that patients can indeed benefit from participating in trials, even when there is no clinical improvement in their condition (see for instance Timmermans, 2010), prompting Will and Moreira (2010) to argue that "ethics committees may do well to acknowledge the ways in which participating in trials may provide forms of care that are valued by patients, rather than seeking to maintain a rigid distinction between relationships for the purposes of research and those inherent in clinical practice."

In addition to *individual* patients potentially benefiting from participating in trials, there is a growing number of examples of patients engaging in the clinical research agenda for their *collective* benefit, a process that has been termed 'evidence-based activism'. Recent empirical research demonstrates such activism taking place in clinical areas as diverse as Alzheimer's disease (Moreira et al., 2014), Attention Deficit Hyperactivity Disorder (Edwards et al., 2014) and childbirth (Akrich et al., 2014). Other notable examples of patient activism include HIV/AIDS research, where patient groups were influential in changing the FDA approval processes to enable faster access to experimental treatments (Marks, 1997; Faulkner, 2010), and oncology, where "patient groups have come to reject the notion that they are the silent objects of therapy, charity, and research, and have consequently demanded and received a place as participants at the clinical research table" (Keating and Cambrosio, 2007). These examples highlight the ways in which patients have made themselves "part and parcel of the networks of expertise on their conditions" (Rabeharisoa et al., 2014). No longer viewed merely as passive research subjects, patients are taking an active role in shaping clinical research, and in the process creating new models of collective enquiry and co-production of knowledge.

The relationship between patients and clinicians, and the increasing role of patients in driving the clinical research agenda, are clearly key aspects of the conduct of clinical trials. It would be naive, however, to assume that these are the only factors shaping the way clinical research is conducted, reported and used, because commercial considerations inevitably also have a significant role to play. Most clinical

research is funded by the private sector (Will, 2010), and there is a large body of research showing that commercially-funded trials are more likely to show positive results (Brody et al., 2005). Bias in favour of commercial sponsors can enter trials at every stage, from research design (including the use of inadequate comparators or inappropriate patient groups), to trial conduct (for instance stopping trials early or selecting favourable follow up periods) and reporting and publication bias, including the suppression of negative results, 'data-dredging' for significant differences, and multiple publication of trials with positive outcomes (Brody et al., 2005; Sismondo, 2008; Will, 2010). Various attempts have been made to address these issues; for instance, the CONSORT statement aims to improve reporting standards, and compulsory trial registration aims to reduce publication bias. There are still concerns, however, that the validity of clinical research is undermined by the influence of pharmaceutical companies: for instance, there was recently a high-profile media campaign concerning Roche's failure to publish all of their trial results on the anti-viral drug Tamiflu (Goldacre and Heneghan, 2014).

Irresponsible, and even underhand, behaviour on the part of pharmaceutical companies is perhaps unsurprising, given that as commercial organisations they exist to make a profit, not to provide a public service. However, the clinical research for commercial trials is generally carried out and published by academic researchers, who in principle have no interest in presenting a biased view of the results. It is therefore necessary to consider the relationship between the researchers themselves and the companies sponsoring the research, and how this could affect the way the trial is conducted and reported. It is tempting to assume that the relationship is a simplistic one - the pharmaceutical company is paying the bills, so the researchers ensure the study shows the desired results. This may overstate the extent to which bias is premeditated and deliberate, however, and Sismondo (2008) suggests that instead, the funder's influence over research should be interpreted in more behavioural terms, arguing that "sponsorship … creates subtle influences through the building of relationships that lead researchers to see the pharmaceutical companies with which they interact, and their products, in a more favourable light than they would otherwise." It seems likely that in fact both types of bias are

possible, and that commercially-sponsored trials can be affected by both outright, cynical attempts to mislead, and by more hidden biases stemming from the dynamics of the relationship between the sponsoring company and the individuals conducting the research.

This brief review of the sociological literature demonstrates that far from being the neutral tools of EBM rhetoric, RCTs are in fact complex and fluid social processes that introduce new and shifting dynamics between patients, clinicians and companies. Clinicians must reconcile their conflicting roles as caregiver, researcher and funding applicant/recipient; individual patients must make sense of their participation in research that poses as medical care; and collectively patients can also engage in the process of generating and utilising the knowledge that this research generates. Commercial organisations, meanwhile, are challenged to generate profit by increasing clinical knowledge in a socially responsible way, and to balance calls for greater transparency with the need to restrict access to commercially-sensitive information. In the rest of this chapter I will examine how these social dynamics play out in UK cell therapy trials, using the framework provided by the existing literature as a starting point. This framework has certain gaps, however, that I intend to address. Firstly, much of the existing literature looks at non-UK trials, often focussing either on the US, which has a very different healthcare system, or developing countries, where trials have very different social dynamics and ethical considerations. Secondly, much of the literature focuses on the role of large pharmaceutical companies rather than smaller commercial enterprises, and the main sociological critiques tend to focus on drug studies rather than complex interventions or advanced therapies (see for instance Busfield, 2006; Davis and Abraham, 2013; Sismondo, 2008). My work, therefore, both draws on and extends the existing literature, by providing a detailed examination of how the social dynamics of trials operate in an under-researched context: UK-based, largely publicly-funded trials of experimental biomedical treatments.

4.2 Clinicians as researchers: the cell therapy 'pioneers'

A distinctive feature of cell therapy trials in the UK is that they are predominantly publicly-funded, with the majority sponsored by academic institutions or NHS trusts. Furthermore, even those trials that are funded or sponsored by companies tend to have a strong link with a clinical site or individual clinician; for instance, ReNeuron has developed close links with a clinical neurology department in order to facilitate trials of its hESC-derived treatments. Thus, almost all cell therapy trials could be described as 'investigator-led', in that the treatment is being developed by or in collaboration with the clinicians involved in the trial. This contrasts with the usual model for drug trials, which tends to involve a new drug being developed by internal research teams at a pharmaceutical company, which then searches for suitable clinical sites for trials - a more 'arm's length' approach that was only apparent in one of the trials I reviewed during my fieldwork. There are two main factors raised in the literature that could account for this, the first being that, as discussed in the introductory chapter, Big Pharma has thus far been reluctant to invest in clinical cell therapy research. Secondly, as highlighted in the previous chapter, the majority of cell therapies being trialled in the UK require relatively invasive procedures for either cell harvesting, delivery or both, and as Foley and Whitaker (2012) highlight, this clinical complexity necessitates close cooperation with clinicians to ensure the treatments are workable in a clinical setting. For both of these reasons, then, it is perhaps unsurprising that cell therapies being trialled in the UK are generally being developed by publicly-funded, clinically-led teams. In addition to these reasons indicated by the existing literature, however, my findings suggest that there are also other factors that tend to favour investigator-led trials, and that this has both practical and sociological implications for the field.

4.2.1 Practical implications of investigator-led innovation

The development of cell therapies is an arduous and uncertain process, requiring long-term attention and dedication without any guarantee of commercial success. This does not lend itself to commercial development, as exemplified by the following quote from Interviewee 13 (a scientific researcher):

> "Most advances require a dedicated ... individual who absolutely dedicates him or herself to it, and will take the time to do it properly. However much you can say yes … we're on the verge of a historic advance, it needs a,b,c and d, let us … employ people to do a,b,c and d and it will get done, it won't. It's too complicated and there's too much application to detail, there's too much frustration to be endured." (INT13)

The development process itself, then, appears to lend itself to cell therapies being progressed by dedicated clinical-academic researchers. This was certainly evident for many of the trials I examined, which often appeared to be driven forwards by an individual clinician whose personality and ambitions were key factors in the success of trial. As Interviewee 3 put it when describing the role played by the clinician who was the Chief Investigator for the trial she managed: *"there's this sort of personality that's helped to drive it."* In some instances it was not an individual, but rather two or three people working together who formed this core driving force behind the development of a therapy. For instance, Interviewee 2 (a scientist) described the long-term partnership between himself and a clinical colleague as a crucial factor in the ongoing development of the treatment, and my observations at the ENABLE trial site suggested that the success of that unit was made possible by long-term collaboration between three individuals (a clinician, a research scientist and a cell manufacturer). These individuals, or small teams, have a resilience that helps them to survive and move forwards in what is often challenging terrain, a struggle exemplified by the emotive way that Interviewee 13 described his experience over the years:

> "It's a struggle to survive, but we're used to it. I've lived on the battlefront for I don't know how many years." (INT13)

It may be that an investigator-led innovation model, linked to the careers of individual or small teams of clinicians and academics, may be more suited to this prolonged 'struggle' than a commercial model, which of necessity must generate results, and thus profit, relatively quickly.

Although this investigator-led model of innovation may create the necessary conditions for sustainable, long-term translational research in cell therapies, it also has certain practical implications for the field. Investigator-led trials are not in themselves unusual, however they would not traditionally be associated with early-phase drug testing, which is in practice what many cell therapy trials have become under the ATMP regulations. This means that the investigators setting up and running these trials are often unfamiliar with the regulatory processes involved, as exemplified by these quotes:

> "It was so easy in the past to set up a trial … academic trials didn't have much in the way of monitoring and all that stuff we take for granted now." (INT4)
>
> "Experimental therapy, new therapies, academics taking things to clinic - you know, if we're going to do that we need a clinical trials unit. Whereas traditionally of course people worked in the lab, and then clinical trials were really done by Pharma" (INT7).

The importance of trials expertise is highlighted by the contrasting views of Interviewee 10, who had held a senior position in one of the Clinical Research Networks, and therefore had significant prior experience of trial set-up. He did not feel that the process of setting up the cell therapy trial had been unusually difficult, which he ascribed mainly to his previous experience in the area, as exemplified in this quote about getting ethics approval:

> "I suppose I'm pretty familiar with ethics committees, and I thought that went pretty well and was straightforward." (INT10)

For those without this previous experience, however, trial set-up can be a daunting process, as I saw during my ENABLE fieldwork. The ENABLE protocol was written by a research scientist who had no prior understanding of trial design of feasibility issues, and she explained to me that this made her feel out of her depth, and she was extremely relieved when a trial manager was recruited to take over from her (Field notes 16/04/15). Hers was not an isolated experience: a number of interviewees felt that their inexperience had hampered the process, or resulted in aspects of the trial being more difficult than necessary, as exemplified by this quote from Interviewee 4:

> "I think because it was such a big step, and so unfamiliar to me, I did what a lot of people do in those circumstances and just sort of made it a bit too complicated." (INT4)

It seems, then, that although small clinical-academic sites are in some ways the ideal locus for the long-term development of cell therapies, they are also not generally well-equipped to undertake the clinical testing that is such a crucial step in the innovation process.

4.2.2 Reconceptualising research vs. care

As well as the practical problems created by clinical-academic departments undertaking a role traditionally undertaken by pharmaceutical companies, investigator-led innovation also has sociological implications. Most notably, there is a distinctive research vs. care dynamic that arises from investigators being so closely involved in the trials process. The tensions between research and care described in the literature tend to arise from clinicians undertaking research in addition to their usual role as a caregiver, and drug trials generally involve clinicians trialling treatments that they themselves have not developed, and that may in fact be at odds with established forms of care that they strongly believe in. Cell therapy trials, however, are very different, in that they are predominantly undertaken by clinicians who have a close relationship with the treatment being developed, indeed they may have dedicated a significant part of their career to the research. Furthermore, although the treatments being trialled are often very experimental, and little is known about their likely efficacy or side effects, they are also often the only treatment option for very sick patients. Thus, the research vs. care dynamic in cell therapy trials differs from that seen in drug trials, firstly because those providing clinical care are often personally invested in the research, and therefore experience fewer tensions between the two, and secondly (perhaps consequently) because to some extent these tensions can be reconciled by reconceptualising research *as* care.

My findings suggest that when investigators are professionally (and even personally) invested in the treatment being trialled, they have more of a vested interest in the trial being conducted well, and in the results being accurate, than they

might for a commercially-sponsored drug study. This was particularly noticeable during my observations of ENABLE meetings, where it became apparent that the whole team made a considerable effort to ensure the trial protocol was followed correctly. To give one example, Mr. Hamilton was very careful to avoid being 'un-blinded' by inadvertently finding out which patient had been given a particular treatment (Field notes 18/12/14). This required active effort on his part, because he needed to avoid seeing identifying information on the videos taken during the surgery and the scans and histology results. It also relied to some extent on his 'forgetfulness', because the procedure for harvesting the cells was slightly different for each treatment, so theoretically he could remember which patient had been given which cells at a later date. In fact, as Amy pointed out to me, the impact of him being un-blinded would have been minimal as he was not involved in the assessment of outcomes. However, he was concerned that it could still have some effect on the trial, because knowing which cells a patient had been given might have affected his treatment of them during recovery (even at a subconscious level). This dedication to maintaining the integrity of the blinding stands in stark contrast to the numerous examples in the literature of clinicians attempting to subvert the randomisation or blinding procedures.

The ENABLE team were so keen for the trial to be conducted well, in part at least, because they were genuinely in equipoise about the treatments being tested. This was evident in the way they discussed the likely outcome of the trial, using phrases such as 'if it turns out [treatment type] works better', and also in their discussions around the time of the first data monitoring committee report, when they were frustrated not to be able to see which treatment was 'winning' (due to there being no interim analysis allowed for in the protocol). The final 'unveiling' of the results was clearly something that was awaited with anticipation, because the team were genuinely uncertain about which treatment would 'win'. It must be noted, however, that the ENABLE trial was testing three different versions of one cell therapy, and as such could be seen as merely refining the treatment the team already believed in. Their perspective might thus have been different if 'their' cell therapy was being tested against an alternative that they were less convinced by.

Nevertheless, it suggests that they were genuinely agnostic about the results of the trial, and thus were committed to doing the research properly so that the results would be 'right', rather than trying to subvert the process so that it would 'prove' something they already believed to be true, or to give certain patients a treatment that they 'knew' to be better. This outlook was mirrored by many of my interviewees, who generally described their trials as a way to understand more about the treatment, rather than to prove it worked (an issue I will return to in Chapters 6 and 7). Again, this contrasts markedly with the descriptions of commercial trials in the literature, where the focus is often on getting the 'right' result from a commercial perspective rather than a result that is scientifically/clinically accurate.

Close involvement with the treatment being developed, and a genuine belief in the objectives of the trial, would appear to blur the boundaries between the roles of caregiver and researcher, making it easier for clinicians to reconcile their competing demands. This is further facilitated in many cell therapy trials by a belief that participating in the trial is in the best interests of the patient themselves. The sociological literature suggests that one of the main ways that patients benefit from trials is by gaining access to treatments they would not otherwise have been able to afford - a finding from US case studies which at first glance does not appear to be directly relevant to the UK, where healthcare is free at the point of use. In the case of cell therapies, however, few of the treatments being trialled would be accessible to patients outside of a trial, either because they are unlicensed or because they would not be funded by the NHS other than through a clinical trial. Cell therapy trial participants are always patients, rather than healthy volunteers (of which more below), so clinical trials could therefore be the only way for them to access a promising new treatment, and could in many cases be life-saving.

There were many examples in my fieldwork of clinicians seeing trials as a way to ensure the best care for their patients. For instance, the ENABLE team were keen to maintain a portfolio of different trials, which enabled them to continue offering their treatment to patients regardless of commissioning decisions or commercial developments in the field. Mr. Hamilton was even keen to expand the site's capacity for trials because it would help him to treat more patients in the clinic, stating: *"I'm*

the person in the clinic who sees patients who need this treatment" (Field notes 21/05/15). Likewise, Interviewee 17 explained that the rationale for his trial was to make the treatment more widely available to patients. Taking this a step further, a clinician at a cell therapy clinical conference expressed the view that the process of being in a trial might be beneficial in itself, by giving patients hope, making them feel invested in the development of new treatments, and helping to prevent stem cell tourism (Field notes 01/05/2015). In this context, then, it is unsurprising that clinicians involved in cell therapy trials do not appear to experience a significant conflict between conducting research and caring for their patients, because to a large extent the research is actually facilitating or enabling that care.

It is tempting to conclude from this discussion that the rigid trials process, with its focus on eliminating subversion and bias, is less necessary in an academic context where investigators appear to be fully supportive of the research. Academic commitment, however, does not by any means eliminate all the problematic aspects of trials that have been highlighted in the literature. For instance, although academic investigators may have little incentive to manipulate trials for commercial gain, many of them believe strongly in the treatment being trialled, and this could provide an equally strong motivation for attempting to sway the outcome (albeit unconsciously, as Mr. Hamilton's desire to remain blinded demonstrates). Furthermore, many academic careers are bound up in the treatments being trialled, and although most do not have a commercial aim, they do need to secure further funding, or simply justify the commissioning of the treatment that they want to provide to their patients. Again, this creates a potential motivation for trials to be manipulated, either deliberately or sub-consciously, and also encourages investigators to present trial results in the best possible light. For instance, Interviewee 7, when describing the results of previous trials in his area, explained that although they failed to show a positive treatment effect, this was largely due to failures in trial design rather than a genuine lack of efficacy. Although this was not necessarily incorrect, it was clearly not the only way to interpret the trial results, and has obvious similarities to the examples in the literature of pharmaceutical companies attempting to bury or 'spin' negative results. We can see, then, that despite most cell therapy trials being an

academic rather than a commercial endeavour, the conditions which create issues such as publication bias and data dredging are still very much present.

Just as the investigator-led model does not eliminate the possibility of bias and subversion in trials, it also does not entirely remove the conflict between research and care. Although my findings clearly suggest that the research vs. care dynamic in cell therapy trials is very different to drug trials, this is not to say that there are not still conflicts between the two. During my ENABLE fieldwork there were a number of instances when the team struggled to balance the needs of the trial on the one hand and the best interests of the patient on the other. For instance, in one meeting there was a long discussion about what window of time should be used for the procedure required to assess the 12-month outcome: a wider window would be more convenient for the patient (giving them more flexibility over when to come back to the hospital), but a shorter window would be better for the research (giving more precision to the findings). In another example, the team spent a long time discussing whether an additional biopsy would have any clinical benefit (e.g. providing more information for the patient themselves, or even having a therapeutic effect), or whether it was solely being undertaken for the research. It was notable that during this discussion Mr. Hamilton stated unequivocally that his priority was the clinical needs of the patient, saying: *"the surgeon needs to forget the trial, and treat the patient appropriately"* (Field notes 16/07/15). Although this kind of dilemma is not unique to cell therapies, it is pertinent that many cell therapy trials require the patient to go through inconvenient or invasive procedures, such as biopsies or scans, in order to measure outcomes. The treatments themselves can also present a clinical challenge, requiring patients to undergo invasive procedures, sometimes with no guarantee that the cells will grow sufficiently, and as we shall see in the next chapter, this conflict prompts some clinicians to adapt trial protocols to protect the needs of patients. Thus, despite most clinicians being fully supportive of cell therapy trials, the research can still conflict with the clinical care of patients.

It is interesting to consider these findings in the context of the increasing drive for the NHS to host more research, which, as Will (2011) highlights, has been justified through "an appeal to the 'benefit' for patients and staff in the combination of

research and care, a multiplication of value through clinical trials." Will suggests that by assuming that research brings benefits to both clinicians and patients, this policy "cuts across an assumption in ethical discourse that clinical work is distinct from experimental work because of their different aims." The assumption behind the NIHR and the CRN, then, is that research does not need to conflict with care, but rather can be an enhanced form of care. This certainly seems to align with my finding that clinicians involved in cell therapy trials often appear to reconceptualise research *as* care, thus to some extent reconciling the conflict inherent in their dual roles as researchers and caregivers. But this does not completely eliminate the conflicts between the two, and in fact the specific characteristics of cell therapies create new ways in which the rigidity of a trial protocol can be at odds with the clinical needs of a patient. It is also important to recognise that the 'value' generated for clinical staff involved in trials is not a neutral one: the altruistic motivation of developing treatments to benefit patients is of course one factor, but many academic careers and reputations are also bound up in the treatments being trialled. There is still a need, then, for a robust ethical framework that protects the clinical needs of patients first and foremost, even as it recognises the ways in which those needs are sometimes aligned with the needs of clinical research.

4.3 Patient-participants: the 'raw material' of cell therapy trials

In order to fully understand how the research vs. care dynamic manifests in clinical trials, we cannot only consider the perspectives of the clinicians undertaking the research and providing the care, we must also consider the experience of those participating in the research and receiving the care. As discussed in Chapter 3, all the trials currently underway in the UK involve patients, despite many being Phase 1 trials that usually involve healthy volunteers. This is partly because these treatments are so experimental, meaning there would be serious ethical concerns about administering them to healthy individuals who have no possibility of benefitting from them. There is also the issue that many of these treatments are produced to target a specific problem in a specific patient (such as T-cell therapies that are primed to target a specific tumour, or neural cells intended to replace dopamine-producing

cells in the brain). In some cases, then, it would not even be possible to produce the therapy using cells from a healthy volunteer, and even those that could be produced could not necessarily be tested for safety, as toxicity could be directly linked to the condition being treated. Finally, many cell therapies involve invasive procedures for harvesting or delivering the cells, which would raise ethical concerns about using healthy volunteers in trials, to say nothing of the likely difficulties of recruiting them.

Unsurprisingly, none of the interviewees mentioned the possibility of using volunteers in Phase 1 cell therapy trials, and indeed Interviewee 12 explicitly questioned whether this could ever work:

> "I don't think there's any ATMP that's ever going to be developed that's going to go into normal individuals as a Phase 1." (INT12)

Furthermore, not only are participants in cell therapy trials patients rather than volunteers, they tend to be the poorliest patients - i.e. those with the poorest prognosis, who have exhausted other treatment options. Again, this reflects the highly experimental nature of these treatments, which means there is an ethical need to reduce risk as much as possible, as explained by Interviewee 5:

> "The patient population we will be treating have a life expectance of two to three months, so it's a clinical irrelevance that remote risk." (INT5)

This raises important questions about how the trials process frames patients, particularly in terms of managing risk, and how this relates to the role of the patients themselves in assessing the level of risk they are prepared to take. Before looking at this, however, I shall discuss how patients might understand the benefits of taking part in cell therapy trials, and the extent to which these trials present distinctive issues in terms of therapeutic misconception.

4.3.1 The appeal of stem cell trials

Despite the potential risks involved, patients are often extremely keen to take part in cell therapy trials, and in particular trials using stem cells. Stem cells have the appeal of sounding cutting-edge and offering a potential 'breakthrough' treatment -

as a clinician involved in trials for MS said: *"drugs don't have the words stem cell in them"* (Field notes 01/05/14). The appeal of stem cells is often due to the combination of a very debilitating disease and a lack of other treatment options; for instance, Interviewee 3 described being inundated with phone calls after a newspaper article was published about the stem cell trial she managed:

> "I think most of the people who were contacting us were people with [disease area] who had undergone years of ineffective treatment, or were facing major surgery. And their options were becoming severely limited. And you know, the hope that this newer treatment might be something ... that would be able to help them personally." (INT3)

Trials of stem cell treatments for less serious diseases can also see similar levels of enthusiasm; for instance, the ENABLE trial team said that the phone hadn't stopped ringing with people wanting to take part, excited about the fact that one of the treatment arms involved stem cells, and saying 'use me as a guinea pig' (Field notes 21/11/13). In this case, the specific appeal of stem cells is emphasised by the fact that at least one patient withdrew from the trial when they realised they weren't guaranteed to get stem cells, even though both arms of the trial involved cell therapies, and the non-stem cell arm was actually the more proven therapy.

Enthusiasm for new, advanced treatment options means that many cell therapy trials do not struggle to recruit - indeed for ENABLE the problem was actually how to avoid over-recruiting, and thereby overloading the cell manufacturing facility. However, like other aspects of cell therapy trials, this was far from a universal experience, and there were other examples in my fieldwork of trials struggling to recruit. For instance, one clinician described difficulties recruiting to a trial where the treatment had to be administered within seven days of the patient experiencing an acute event. She felt that this was a very emotional and risk-averse time when patients were unwilling to consider an experimental treatment, meaning the involvement of stem cells was barrier rather than a draw (Field notes 19/01/13). In other cases, the complexity of the process was felt to be off-putting; for instance,

Interviewee 9 explained that he would try to simplify the treatment protocol in future trials to help recruitment:

> "It was very complicated, and it was quite hard to recruit to - it was a lot for the patients to go through. And so we definitely want to progress, but actually we'd quite like to make the whole thing a lot simpler." (INT9)

Here we can see that using the treatment during the trial can help clinicians understand how it works in a clinical setting, which could help them adjust the protocol to facilitate future trials and longer-term clinical use.[10] We can also see that the appeal of a trial, and indeed of the treatment itself, is likely to be affected by the difficulties associated with the treatment itself, as well as the severity and acuteness of the condition and the other treatment options available.

In addition to the availability of other treatment options, the availability of other trials can also affect how easy it is to recruit to cell therapy trials; for instance, Interviewee 11 explained that:

> "There were some [clinical area] Research Network trials going on too that were conflicting, and the problem was they had shorter time windows. So if they passed over a potential patient for that study and considered them for ours, and they ended up basically screen failing for ours, [then] they'd lost the opportunity to put them in the other trial." (INT11)

Interestingly, one Interviewee described this as being a particular problem in the UK, where the CRNs are specifically tasked with improving patient access to trials:

> "In the US, most sites were only running one or two studies at their site, [but in the UK] we have a very healthy portfolio of both complex and simple studies, so most of our sites were running

[10] I will discuss this issue of 'learning through doing', and the challenges it poses in a clinical trials context, in Chapter 6.

> about 10 studies, and patients were being put into simple studies which then meant that they couldn't go into this study." (INT10)

In another example, competition for trial participants was mentioned in the context of drug development taking place in the same area, suggesting that cell therapies do not only face the challenge of needing to be more effective than drugs, but also of accessing the patients to prove this in the first place:

> "There are only so many patients with [disease type], and there are a lot of drug developments going on. So it's seriously the case that there might not be enough people around to support all the drug trials that are sort of happening and being set up" (INT4)

It seems, then, that although recruitment to cell therapy trials, and in particular stem cell therapies, can be very easy in some cases, this is in no way universal. In fact, there are a number of interacting factors that could affect recruitment, including the size of the patient population, whether the disease is acute or chronic, the invasiveness and complexity of the treatment, the availability of other treatments, and competition from other trials.

As well as these practical issues affecting trial recruitment, the appeal of the term stem cell is also ethically problematic when considered in the context of the therapeutic misconception. The fact that cell therapy trials are all conducted with patients means that even in the earliest Phase 1 trials there is theoretically some possibility of benefit, and, as discussed in Chapter 3, even those trials that do not have efficacy as an outcome measure do at least have some possibility of it. This point was reiterated by a clinician involved in a trial of a very experimental cell therapy, who explained that even though the trial involved patients who were not expected to respond at all, some did in fact show improvement (Field notes 01/05/14). The concept of therapeutic misconception is thus slightly different for cell therapy trials, because even in the earliest trials there is a possibility that individual patients might see some benefit. However, there is also a concern that because these trials often target the poorliest patients, there is a risk that desperation could make them overestimate the likelihood of the treatment benefiting them. This is particularly likely given the media hype surrounding stem cells, which is out of step with anything

that has yet been proven clinically. Furthermore, the risks associated with such experimental treatments are potentially much greater than those typically seen in drug trials, and again the therapeutic misconception suggests that patients are likely to underestimate these risks. Finally, given the considerable scientific uncertainty around stem cells, and cell therapies in general, it is clearly very hard to achieve properly informed consent for trials. The therapeutic misconception is therefore an important concern for cell therapy trials, and makes it difficult to balance the rights of the patient to access potentially life-saving treatments on the one hand and the ethical imperative to protect them from harm on the other. In this context, the agency of the patients themselves is of particular interest, as is the way trial protocols frame patients in order to 'control' risk and data accuracy. I shall now move on to consider the balance between these two competing perspectives of patient-hood.

4.3.2 Framing patients, framing trials

My fieldwork highlighted two key components to the way in which cell therapy trials frame patients, with the most important being the management of risk. This is exemplified by this quote from Interviewee 1, who felt that the inclusion criteria for his trial were extremely rigid, but rationalised this as being necessary when trialling an experimental and potentially dangerous treatment:

> "I suppose the treatment could potentially be toxic. If someone's heart is severely damaged you shouldn't do it, it's probably dangerous - and certainly with an experimental therapy you shouldn't be doing it." (INT1)

Interestingly, in this case the inclusion criteria were being used to mitigate risk by limiting treatment to patients who were clinically able to cope with it, which contrasts with the examples discussed earlier of trials focussing on the poorliest patients (although the trial overall was being conducted with patients who had a life-threatening disease that had not responded to other treatments). In addition to the control of risk, inclusion criteria are used as a way to 'control' the data generated by the trial, to make it more manageable or more acceptable. This was very apparent in the ENABLE trial, where there were frequent discussions about whether to include

patients with certain previous treatment, or presenting with certain clinical conditions. On the one hand the team was keen to make the trial population as wide as possible, so that it was representative of the general patient population, as this was seen to be essential for the results to be credible for future publication, marketing authorisation and reimbursement. On the other hand, however, they were reluctant to introduce too many variables into the trial population, worrying that it would make it harder to 'see' the effect of the treatment (Field notes 22/01/15 and 19/03/15). These competing priorities were never definitely resolved, but were part of the ongoing negotiations that took place throughout the trial.

The use of strict inclusion criteria to minimise risk and control the data is complicated by the second important component of the way that trials frame patients, which is that the rigidity enforced by trial protocols doesn't accurately reflect the complexity of clinical reality. This issue was highlighted by Interviewee 1, who explained:

> "Trial entry can be very rigid, and sometimes inappropriately rigid … I guess it's very difficult, you've always got a cut off and somebody's always going to fall 1% below. And you think does it really matter, and the answer is probably not. But I suppose that's just the reality of trials." (INT1)

This situation occurs because clinical trials enforce a binary approach - the patient is either included or not. This means that their clinical situation must be reduced to a series of binary answers as well - they either meet each inclusion criteria or they do not, with no grey areas in the middle. Trial protocols thus make sweeping generalisations about which patients will be suitable for the trial, whereas in reality each patient has a unique medical profile, including, amongst other things, their specific combination of symptoms, prognosis, co-morbidities and previous treatments.

The ongoing negotiations in the ENABLE team meetings about which patients to include in the trial suggest that despite the rigidity suggested by the protocol, cell therapy trials can actually involve quite nuanced clinical assessments of patients. This was also apparent in a number of my interviews; for instance, Interviewee 3

described a multi-disciplinary clinical team being assembled to discuss each patient's clinical history to assess whether the treatment being trialled was the best approach for them, and Interviewee 12 described a similar process:

> "We've had a multi-disciplinary team in meetings that have 20, 30, 40 people to tell whether a patient should have one of these, and whether it's in their best interest." (INT12)

It appears, then, that there are in fact two different ways of framing patients in clinical trials: firstly, the rigid, binary generalisations dictated by the trial protocol, and secondly a more nuanced clinical decision, based on a much more holistic view of the patient.

In conjunction with the way that cell therapy trials, and trialists, frame patients, my interview data suggests that patients also have a role in framing trials. This can start with patients driving the development of the treatments themselves, as explained by Interviewee 7:

> "Probably one of the biggest impetuses comes from the patients. So the patients are aware of the fact that there are very good treatments out there for [disease], but they don't cure them, they have side effects. And so, you know, these young patients in their 30s and 40s who are looking at 40 or 50 years of treatment, knowing there will be complications down the line, they are looking for something that's better than what's out there at the moment." (INT7)

In this case, patient groups appear to be framing the cell therapy treatment in a particular way: as a distinct alternative to the drug options currently available to them, and with the potential to be more like a 'cure'.

The way that patients frame a cell therapy can potentially conflict with how the protocol frames it; for instance, Interviewee 17 explained that the strict entry criteria for his trial required patients to have exhausted all other treatment options. He felt this could in fact disadvantage well-informed patients who had actively

chosen not to try existing, relatively ineffective, treatments, but would willingly risk an experimental treatment that had the potential to actually cure them:

> "People are in that mindset because of the way clinical trials work, if you've been subjected to surgery before and lots of interventions and it hasn't worked it kind of feels risk benefit wise OK to take the next step and try an experimental treatment. Whereas if you have the same condition but you haven't had all those treatments first, is it ethically OK to go from there to there without doing all the treatments?" (INT17)

He went on to reflect that the current trials process limits patient agency by making assumptions about the relative risks and benefits of them participating in the trial, rather than allowing them to make the decision:

> "Our model is imposed by us looking at the patient and not asking the patient – 'I've chosen not to do the [existing treatment] because I don't want to - I would happily go from here to here, but I'm not doing all of that.' So it's how do you bring the patient into the ethics" (INT17)

This view was also expressed by Interviewee 7, who felt that although there needed to be protections in place, it could be argued that an overly-cautious approach was failing to incorporate the patients' own views about acceptable levels of risk:

> "The charity would say that they feel that generally the regulatory authorities and the people who if you like control trials are too conservative, and think they're protecting the patients. [But] the patients themselves would probably be prepared to go for things earlier, with the realization that there is slightly more risk".

Thus, it appears that by framing a treatment in a certain way, i.e. as a highly-risky last resort, a trial protocol can fail to recognise alternative framings that may be relevant and important to patients.

These findings suggest there is a need for trial protocols to accommodate the way patients themselves frame the treatment, and the trial. However, despite the

obvious benefits of allowing patients to influence decisions about the development of treatments that could benefit them, interviewees also highlighted the difficulties involved in this. Interviewee 7 explained that there was a tension between the importance of protecting the patient and the desire to take their priorities into account:

> "Now it can get a bit on your wick … because they're sort of saying there are no barriers just get on and do it, and you're saying no, it's not that simple. And if it did go wrong you probably would come knocking on my door and saying why on earth why did you kill my brother with this therapy? (INT7)

He concluded that involving patients in the planning of trials was the only way to reconcile these tensions:

> "I do think that getting patients more involved, asking them what it is they would like to see out of a trial, I think is also going to be important." (INT7)

Another interesting perspective was expressed by a clinician talking about his cell therapy trial, who felt that patients framed their participation in trials as an altruistic act, explaining that:

> "Patients going through this trial are very brave … they know there won't be a direct benefit to them, but they still volunteer … so big respect to them." (Field notes 01/05/14)

He went on to reflect, however, that because patients are generally so enthusiastic about participating, the consent process almost needs to be pessimistic to reduce the risk of overestimating benefits, particularly because going through this trial might preclude them from trials of other innovative treatments in the future. The way that patients frame trials can be problematic, then, in that it can be difficult to balance their understanding, expectations and values with 'objective' or 'expert' judgements about risks and benefits, particularly in such an uncertain and experimental field.

Overall, it is clear that cell therapy trials frame patients in particular ways, which may be at odds both with other clinical perspectives and with the patient's

own priorities. The rigidity of the protocol reduces complex clinical, physiological and social circumstances to a series of binary inclusion and exclusion criteria, which might not align with an individual patient's values and preferences. This aligns with sociological commentaries that have highlighted the ways in which trials configure patients, to the extent that they essentially create the 'objects' that they are investigating (Webster and Faulkner, 2015; Brives, 2013). Not all trials frame patients in the same way, however, meaning that the role of patients in a cell therapy trial cannot be generalised, but has specific characteristics that arise from the interaction of numerous factors, including the type of treatment, the disease area, and the perspectives and aims of those designing the trial. A good example of this is the way that the framing of risks and benefits to patients varies between trials: in some cases, the poorliest patients are specifically targeted in order to reduce risk, whereas in others they are excluded as being more at risk from the treatment. Furthermore, despite the rigidity of the trial on paper, decisions 'on the ground' appear to be made in a much more fluid way, suggesting that the selection of patients to participate in a trial is not nearly as objective as EBM dogma would suggest. Far from being a neutral tool, then, a trial protocol actively creates the objects of the research through a specific framing of patients, it has a direct impact on the likely outcome of the trial. This is complicated, however, by the fact that the objects created by the protocol are not fixed entities, but fluid concepts that can shift and change as the trial progresses.

Balancing this perspective of patients as the *objects* of clinical trials is the parallel discussion of the role they play as *active participants* in clinical research. The fact that in some cases trials appear to be competing for patients suggests that the distinction between research and care is a fluid one for patients as well as clinicians, and that patients may perceive research as being the best form of care for them. The question does not always appear to be whether they want to take part in research at all, but rather which research will best suit their needs - a situation in which the patient appears to be acting more like an active consumer than a passive research subject. This active participation is also reflected in the role of patient advocacy in driving the development of some cell therapies, demonstrating that at both an individual and a collective level patients are important actors in the process. The

sociological literature on patient advocacy highlights the ways in which patient involvement can help to engender a more socially-robust approach to clinical research and policy-making (see for instance Moreira et al., 2014; C. Edwards et al., 2014), and my findings suggest that this would certainly be the case for cell therapies. There is certainly a good argument for patients having a greater role to play in ethical decisions around cell therapy licensing; for instance, Eichler et al. (2015) make a persuasive case for patient involvement being a crucial factor in adaptive licensing. My interview data also highlights, however, that this is not a straightforward issue, not least because of the need to reconcile the views of *groups* of patients with the needs of *individual* trial participants. Collectively, patients can be involved in shaping the direction of clinical research and the wider ethical decisions involved, but only as individuals can the specific risks and benefits of a trial be considered, taking into account a particular patient's circumstances and values. Importantly, it is at an individual level that the issues of informed consent and therapeutic misconception loom largest, a point that has been raised in other commentaries on cell therapy trials (see for instance Hyun et al., 2008; Lo et al., 2008; and Lo and Parham, 2009). My findings support the concerns these authors have raised: the hype around stem cells, the uncertainty of the science, and the poor prognosis of many patients make informed consent extremely difficult, and increase the likelihood of patients overestimating the benefits and underestimating the risks of trials. Patient agency, then, can be seen as an important but problematic aspect of cell therapy trials, and it is important to recognise the tensions between individual and collective agency, and the fundamental difficulties of balancing individual agency and acceptable risk.

4.4 Commerce and cell therapy trials: friend or foe?

The role of clinicians and patients in shaping clinical research on drugs has generally been dwarfed by the role of commerce. This has not necessarily been the case thus far for cell therapies, but this is not to say that commercial concerns are absent from the field. Around a third of current trials have a commercial sponsor, and the private sector is also involved in other ways, such as the provision of reagents or the manufacture of cells. Commercial considerations are also apparent in the way that

academic institutions conduct cell therapy trials, for instance in the decisions they make about protecting intellectual property, or whether to aim for marketing authorisation. Nevertheless, the role of commerce in cell therapy trials is clearly different from drug trials, not least because the companies involved are very different to the multi-national corporations that dominate drug development, as Interviewee 14 highlighted:

> "A lot of the companies, and I don't mean all of them, but a lot of them are smaller companies. They tend to be spin outs of universities, just sort of smaller start up organisations that have found something that works and they're building a company around it." (INT14)

In some ways, then, the companies involved in cell therapy trials have more in common with academic researchers than corporate drug manufacturers (Maciulaitis et al., 2009), and may even be the same individuals. This issue was raised by the House of Lords report, which described the companies involved as "very small companies or academic groups that have no experience in the field and are overwhelmed by the entire complex regulatory system" (House of Lords, 2013). There is also evidence that lack of experience and/or resources makes small companies less likely to be successful when applying for marketing authorisation (Regnstrom et al., 2009). Rather than functioning very differently to the academic sphere, then, these companies are likely to face many of the same problems in terms of lack of expertise, limited capacity and funding challenges. Likewise, the relationship and power dynamics between these companies and the clinicians and scientific researchers involved in trials will inevitably differ from that described in the literature on drug trials. This section will examine these dynamics in detail, firstly by looking at why commercial involvement is both important and problematic for trials, and then by exploring how the focus on commercialisation can conflict with the clinical-academic model of innovation.

4.4.1 The commercial reality of the trial

The literature reviewed in Chapter 1 highlights access to funding and a credible business model as essential factors in the translation of cell therapies, and many of my interviewees, whether from a commercial or academic background, were very aware of the need for their treatment to be commercially successful. One of the reasons for this was that they felt that public funding is unlikely to be sufficient for the large, highly regulated trials required for ATMPs, particularly for high-risk stem cell therapies, as Interviewee 7 explained:

> "Ultimately when we move to stem cell therapies it's going to go to a company, because you're never going to sustain it academically." (INT7)

This view was also reflected by Interviewee 10 (a clinician who acted as PI for a commercially-sponsored trial), who felt that commercial funding was important in paving the way for further developments in the field:

> "We were sort of the pioneers, even though it was a commercial study. And in that sense, it was quite a good one to take forward because we had those resources ... if you were trying to do this academically it would be really expensive." (INT10)

The economic realities of conducting clinical trials meant that many interviewees accepted the need for cell therapies to be commercially successful, as Interviewee 5 (an academic researcher) put it:

> "It doesn't matter if you can cure all of your patients, unless someone can make money out of it it's not going to go anywhere." (INT5)

This pragmatism was echoed by Interviewee 16 when he considered the role of the Cell and Gene Therapy Catapult:

> "It's clearly set up by a Tory government because their primary aim is actually to generate wealth, but I don't see why that's such a bad thing." (INT16)

This quote highlights both a recognition that cell therapy policy has an economic motivation as well as a public health objective, and also the way that some interviewees at least accepted that this is not necessarily unreasonable.

Some interviewees were not only accepting of the need for commercial involvement, they actually felt that academic researchers could benefit from commercial expertise. For instance, Interviewee 12 said that he would advise anyone setting up a cell therapy trial to recruit someone with experience of pharmaceutical trials. In a similar vein, Interviewee 15 (a clinical researcher) explained that he had previously worked with someone who had a background in pharmaceutical trials, and that this had been very important because in his clinical area they weren't used to the phase model of drug trials, as in the past they had only trialled devices. And it is not only academic organisations that can benefit from commercial expertise: Interviewee 17 (the head of an SME developing a cell therapy treatment) also described benefitting from discussions with a commercial research organisation which had experience of running large drug trials.

Despite recognising the need for, and potential benefits of, a commercial outlook, many interviewees raised concerns that this might conflict with the way that academic researchers are used to operating. Interviewee 7, for instance, explained that having to think about GMP issues from the start can be extremely challenging for scientific researchers:

> "A lot of the questions are very boring and they're not scientifically very interesting. But ultimately they will determine whether your therapy works." (INT7)

Concerns were also raised about the fact that the need to make a profit can be fundamentally at odds with clinical priorities. Interviewee 13 held the strongest views about this, to the extent that he would have liked to completely reject any kind of commercial outcome for his research:

> "For it to be commercial you have to have something patentable that you can sell ... I would be very happy if no patient ever had to pay a penny for what I had done." (INT13)

Other interviewees were more pragmatic about the need for a commercial role in developing treatments, but recognised that in some circumstances this could work against the interest of patients. For instance, Interviewee 7 described a treatment that had initially been developed at his hospital and was then bought by a company, and then put through *"ill-conceived"* trials which failed to show efficacy. The company then abandoned development of the treatment, which meant that patients who were already receiving it had their treatment withdrawn, even though their hospital had originally developed the treatment and they felt that it was benefitting them. He felt that this was an example of the delicate balance hospitals need to tread between developing commercially viable treatments and protecting the interests of patients, concluding that: *"you have to be aware of the commercialisation, but you've got to get it at the right time."* He then went on to describe his concern that the need to commercialise cell therapy treatments could result in treatments becoming unaffordable:

> "My greatest anxiety ... is we end up demonstrating it works well, we develop a stem cell therapy that works incredibly well, we think we've got a wonderful treatment to offer people with [disease] and then suddenly you discover we can't afford it." (INT7)

This quote clearly demonstrates the tensions between the commercial success of a cell therapy product, which might be necessary for it to be developed at all, and the clinical priorities of those involved in developing it.

As well as the tension between commercial considerations and clinical priorities, there can also be a conflict between commercialisation and academic research, particularly when it comes to the publication of results. Interviewee 2 gave a good explanation of the pressures imposed by commercial sponsors, and the struggle that he had to protect what he perceived to be the 'integrity' of the research:

> "You've got the dreaded confidentiality agreements … companies always have their long spiel of conditions, and the one I always cross out is that any result of work that goes on in my lab or that I have contributed to remains confidential and can only be published with company approval. I'm happy to give six weeks' notice before

> anything is submitted, but the data is the data, and it's not going to be kept secret." (INT2)

The issue of transparency also extends to sharing knowledge in the field, which some interviewees raised as an issue with commercialisation, such as Interviewee 5, who was concerned that:

> "Now that commercial interests become involved, people are going to start protecting know how." (INT5)

The lack of collegiality in commercial research also emerged in other ways; for instance, Interviewee 4 suggested that companies can use competition for patients in trials as a way to prevent rivals from being able to test their products:

> "Some of the pharmaceutical companies set up trials to stymie their rivals … they do a trial they don't really have any great interest in, but it means there are fewer patients for their rival with a fundamentally new treatment." (INT4)

In this example, we can see that the interests of commerce are restricting the generation of knowledge, thus limiting innovation, and Interviewee 5 described another way that this can happen:

> "[Cell type] in particular are being heavily commercialised at the moment because some really remarkable results have been generated … And that brings the bad side out, you start seeing people getting protective about reagents, commercial agreements come into place, restricting access to other people, meaning that you have to duck and dive with your process and find alternative suppliers and that kind of thing." (INT5)

These findings suggest that the dynamics of the marketplace tend to work against the sharing of knowledge and resources. Academic research is, of course, not immune to competitiveness or a lack of transparency, however this is to some extent offset by traditions of collegiality and collaboration in academia, and by institutional processes that encourage open access to data (particularly for publicly-funded research). Unsurprisingly, these tensions between the academic and commercial

aspects of cell therapy trials meant that many interviewees had reservations about the demands of commercialisation, even as they understood the importance from an economic perspective.

A further issue that interviewees raised about commercialisation concerned the spread of risks and benefits between the private and the public sectors. There was a general consensus that the early stages of cell therapy development will always have to be in academia, a view summarised by Interviewee 2:

> "I think the development of how to do it has to be done in an academic centre, by specialists in the [specifics of disease area] and the patient assessment." (INT 2)

This was reiterated by Interviewee 12, who explained that the early development of cell therapies tends to be in clinical-academic settings, with companies only becoming involved later:

> "These are still investigator developed products, so they're not coming from pharmaceutical companies. Pharma's buying them, after as early as Phase 1, Phase 2 data, but they're not being developed by them. Because they come out of an idea that someone at the front end has." (INT12)

This is a very different model to that seen in drug development, where typically all product development and trials (from Phase 1 onwards) would be undertaken by the company. Interviewee 12 went on to raise the point that this system works well for companies, because it allows them to 'screen' treatments and cherry-pick the most promising ones for further development:

> "Pharma see it as a new paradigm that saves them money - it de-risks the process if someone in academia is doing an early phase trial and shows efficacy. 1 in a 1000 drugs gets through to Phase 1, because they don't even get that far, but someone has done your Phase 1 and you're buying it at the end of Phase 1, when you've got safety data and you've got some efficacy." (INT12)

What this means, of course, is that the risk is transferred to the public sector, which is funding expensive early trials but doesn't then benefit economically if these trials are successful. The unspoken assumption behind this is that the research will ultimately be of benefit to patients, making this an appropriate use of public funds (this assumption is also one of the motivations for patients taking on the clinical risks of participating in the trial). But if, as we have seen can happen, these treatments are either unavailable (because companies choose to withdraw them because they are not commercially viable), or unaffordable, then this implied contract fundamentally breaks down.

4.4.2 Commerce and the clinic: complementary pathways or competing futures?

In addition to concerns about the effects of commercialisation, some interviewees also questioned whether the commercial route, as represented by applying for marketing authorisation, was even appropriate for their therapy at all. This is partly because some therapies, particularly those that cannot be mass produced, do not appear to fit well with the marketing authorisation model, as explained here by Interviewee 12:

> "On the tissue engineered products ... how would you make it for 200, 400 patients? You couldn't. I don't believe, in the current way that one assesses a drug for a marketing authorisation, that something like a tissue engineered trachea or larynx or oesophagus could get a marketing authorisation." (INT12)

Interviewee 12 went on to explain that he saw difficulties in the enforcement of marketing authorisations for products that have such a complex production process, where it would essentially be the process rather than the end product that would be the subject of the authorisation:

> "We've just seen that an Italian company has got a marketing authorisation for limbal stem cell transplants. I don't know how well that's going to stand up, or indeed if it's defensible … To do a limbal stem cell transplant you have to take limbal cells from the good eye … grow them on a substrate and then implant that

> substrate on the right eye, the bad eye. So in terms of a licensed medicine, if someone just uses a different substrate it's a different medicine." (INT12)

These quotes reflect the misalignment between the commercial focus of much cell therapy policy and the fact that many cell therapies are actually being developed as clinical, rather than commercial, products (discussed in Chapter 3). The impact of this misalignment was very apparent in my observations of the ENABLE trial. The team were keen to continue developing their treatment in a hospital setting, and rather than attempting to commercialise the product their approach was to share their knowledge with other clinical academic sites, encouraging them to develop their own treatments and learn from the early work that had already been done. In one instance, Mr Hamilton arranged a conference of other cell manufacturers to share experiences and ideas, and in his introductory talk he invited attendees to use the work of his team and build on it, asking them to: *"learn from us, but also ask serious questions of the scientists"* (Field notes 23/09/15). This model shares more with the process of innovation in surgical techniques than drug development, with individual surgeons sharing their experience at conferences and in publications, and slowly achieving consensus on best practice.

Overall, my findings suggest that commercialisation is an important factor in cell therapy trials, in large part because of their high cost and complexity. This issue is likely to become even more acute as treatments move towards large Phase 3 trials, which will be unaffordable for the public grant-giving bodies that have largely funded earlier trials. In some ways, the role of commercial actors in trials has been beneficial, as academic researchers who are unfamiliar with drug trials can benefit from the expertise of companies who have more experience in the area. The relationship between commercial and clinical-academic research remains a problematic one, however, despite the fact that most of the companies involved are SMEs rather than large multi-national corporations. One of the most divisive issues is the lack of transparency inherent in commercial research, which is at odds with academic and clinical models of knowledge generation and innovation. As described in the literature, the issue of transparency in commercial trials generally relates to

publication bias: i.e. positive results being more likely to be published than negative results, meaning that systematic reviews will overstate the efficacy of the drug (Sismondo, 2008). My findings suggest, however, that cell therapies may be vulnerable to another problem concerning the publication of results, which is that companies are reluctant to divulge commercially sensitive information about the cells and processes used, and to share the knowledge gained from clinical testing. This lack of transparency, particularly around issues such as cell characterisation, is likely to be problematic when it comes to resolving the major clinical and scientific uncertainties of cell therapies - an issue I will examine closely in Chapter 6. It also poses a problem for the generation of evidence; the EBM framework places systematic reviews of RCTs at the top of the evidence hierarchy, but without a detailed description of the cells used it will be extremely difficult to conduct such reviews for cell therapies. Thus, the demands of commercialisation will make it difficult to interpret, compare and build on the results of trials, raising the question of whether a commercial approach, made necessary in part by the high cost of clinical trials, will in fact hamper innovation in some parts of the field.

This raises a wider question about whether the commercial model is appropriate for cell therapies that are being developed in a clinical context. The ENABLE team's experience provides a good example of the fundamental difference between the two models: their collegiate and transparent approach to developing the therapy, whilst likely to facilitate innovation and adoption within the field, does not lend itself to the development of a commercially successful proprietary product. The ENABLE team were concerned that the commercial model being promoted by policy makers, and in particular by the CGCT, was not appropriate for their treatment, which is relatively small-scale and based in an individual hospital. However, they could not see an obvious alternative route to pursue and felt that the future of the centre, and perhaps of the treatment itself, was therefore extremely insecure. This aligns with the findings of Sanchez et al. (2013), who report that in the US there is a feeling that being forced down a commercial route is limiting for academic-initiated trials. The commercial development model for cell therapies also transfers much of the economic risk of early product development to the public sector, and to some

extent challenges how the risks associated with clinical research are reconciled. As mentioned earlier in this chapter, the risks of clinical research tend to be justified by the potential to benefit many patients in future, but this is of course undermined if the treatments being tested are unavailable to future patients, either because they are too expensive or because the company decides to withdraw them for some reason. Furthermore, clinicians and patients often reconcile the conflicting demands of research and care by reconceptualising research *as* care, but again this is undermined if commercial priorities take precedence over the development of effective treatments.

4.5 Discussion

Using the framework suggested by the sociological literature, my findings suggest that UK cell therapy trials demonstrate many of the social dynamics that have been identified in other types of trials. Despite being more closely involved in the research than their counterparts in drug trials, clinicians involved in cell therapy trials still have to reconcile the needs of the research with their primary role as a caregiver. Patients can struggle to make sense of their participation in cell therapy trials, even as they clamour to have access to the latest treatments, and the therapeutic misconception is if anything heightened in this advanced field characterised by high expectations and great uncertainty. The role of large corporations has so far been limited, but the role of commerce in cell therapy trials is still problematic, and although a commercial approach is important because of the need to finance expensive trials, this can conflict with the academic and clinical priorities of many cell therapy developers.

There are also, however, important differences between the social dynamics of cell therapy trials and those described in the existing literature, which is largely focussed on drug trials. Because the majority of cell therapy trials are investigator-led, the clinicians involved are often heavily invested in the research. This means that they experience the tensions between research and care differently, and to some extent reconcile them by reconceptualising research *as* care (a perspective that appears to be shared by many patients). Investigator-led trials are often hampered by a lack of experience of running highly-regulated drug trials, and although to some

extent this can be outweighed by drawing on the experience of companies, many of these companies are also inexperienced and have limited resources. This also means that the relationship between academic researchers and commercial sponsors is different to that seen in drug trials, with different tensions and power relations coming into play. Finally, the ways in which these trials frame patients, and in particular the specific framing of risk, can be at odds with both an individual patient's priorities and their clinician's understanding of their clinical situation. This suggests that there is an argument for patients, both individually and collectively, having a greater say in decision making, but there are also valid concerns about how far patient agency can be accommodated in such a fast-moving and uncertain field.

Another important issue raised in this chapter is the extent to which the social dynamics of cell therapy trials are both heterogeneous and fluid, with the specific configuration for each trial being highly dependent on the local context. Amongst other things, there can be great differences between trials in terms of the experience of the Chief Investigator (CI), the way that the protocol frames patients, the attitudes and priorities of the patients themselves, and the potential for (and attitudes towards) commercialisation. So, for instance, a trial might be considered risky from a regulatory perspective because it uses an untested cell type, but could still be relatively easy to set up because the CI has experience of drug trials. Such a trial might recruit well because the treatment is not invasive, and it might appeal to patients due to there being no other possible treatments, however, the protocol might frame risk in such a way as to exclude many patients from participating. Conversely, a trial for a relatively well-known and safe treatment might be more difficult to set up if the CI is unfamiliar with clinical trials of medicinal products (CTIMPs), and might struggle to recruit if there are other competing trials or patients are risk-averse at the time of treatment, despite the protocol framing the trial as low risk. Heterogeneity between trials is heightened by the fact that investigator-led trials appear to be driven by individuals or small teams of clinicians and academics, meaning they take place within 'pockets' of innovation rather than a more structured framework or platform, such as exists for cancer trials (as descibed by Keating and Cambrosio, 2012; 2007). This undoubtedly contributes to the fragmentation I described in the previous

chapter, because rather than specific variables, such as the type of cell used, determining how a trial is likely to progress, each trial involves a specific configuration of dynamics between patients, clinicians and commerce, affecting both the success of the trial and the long-term development of the treatment.

The fluid and heterogeneous social dynamics of cell therapy trials must be taken into account when considering improvements that could be made to the trials process. In particular, this is crucial to two key questions raised by the analysis in this chapter: firstly, the extent to which a commercial 'drug trials' model is incompatible with innovation in a predominantly investigator-led field; and secondly, the issue of how patient agency can be accommodated without introducing unacceptable risk. The expense of conducting highly-regulated trials necessitates a commercial approach to cell therapy development, but this often conflicts with, and constrains, progress in academic research, and presents an unacceptable division of risk between the public and private sectors. Current policies for facilitating translation, such as adaptive licensing and risk sharing agreements, all assume that the end goal is a marketing authorisation, but many clinical-academic developers do not feel that this commercial model is appropriate for their treatments. There is currently no alternative model for centres that wish to develop treatments with no commercial intention; options are limited to either conducting full-scale trials, with a view to applying for marketing authorisation, or delivering treatments under the limited confines of HE. My findings suggest that there is an argument for developing an alternative, non-commercial framework that is better aligned with the way many cell therapy treatments are currently being developed, and which could run alongside the current commercial model. This framework would also help to alleviate the difficulties publicly-funded trial sites experience because of their unfamiliarity with drug trials. Such a route, however, would require a different approach to trialling, as full-scale trials would be unaffordable without commercial backing.

There is a need, then, for the development of a more flexible and affordable trials process, which could be applied in areas where there is no commercial aim for the treatment. Such a framework could accommodate a more clinical/surgical style development model, and could also be designed to allow for greater patient agency

in ethical decision making, and to reflect the fact that the different dynamics of an investigator-led field present different challenges in terms of research vs. care, and different risks of bias. There are certainly compelling arguments in favour of such an approach, and in later chapters I shall consider in more detail what this framework might look like. It is important to note, however, that there are also risks that must be considered. As we have seen in this chapter, the clinical-academic development model does not eliminate the possibility of bias or misconduct, and the issues of therapeutic misconception and informed consent are particularly problematic in this area. The challenge, then, is to create a more socially-robust, patient-centric trials process without exposing patients to unacceptable levels of risk, or compromising the credibility of the evidence generated.

5. Doing cell therapy trials: a "poisoned chalice"?

One of the most striking things I heard during my fieldwork was Interviewee 3, a trial manager who had worked on a relatively straightforward cell therapy trial, describing the study as a *"poisoned chalice"* (INT3), and Interviewee 4, the clinician involved in the same trial, reflecting that *"if I were to do another trial … it would kill me."* These negative, emotive descriptions of the experience were not unusual: as we saw in the previous chapter, most interviewees described the trialling process as a struggle or a battle, and gave many examples of the various difficulties and frustrations they faced. Clearly, then, the trialling process for cell therapies is experienced as problematic by those involved; however, I was also struck by a question from a clinician attending an MRC course on cell therapy trials: *"I'm struggling to see the issue here - aren't regulations the same for all drugs? Why are stem cells different?"* (Field notes 01/05/14). On the face of it this is a valid question - although cell therapies do have a number of characteristics that make them challenging from a translational perspective, it is not immediately apparent that these would be specifically problematic in a clinical trial (as opposed to any other type of clinical use). Furthermore, as I discussed in the previous chapter, many cell therapy trialists have little or no experience of clinical trials at all, and certainly not of CTIMPs. It is thus not necessarily clear how much of the struggle they describe (and that is reported in the literature) is due to distinctive characteristics of cell therapy trials, and how much is simply a result of unfamiliarity with the trials process.

Although trialling has been identified as a key barrier to translation (see for instance House of Lords, 2013; Webster and Faulkner, 2015), the majority of the literature does not directly address the issue of why, and indeed whether, this is a particularly difficult area for actually conducting clinical trials. Papers discussing the difficulties with cell therapy trialling have tended to focus instead on challenges to do with scientific uncertainty, such as the applicability of animal models or uncertainty about mode of action (an issue I will address in Chapter 6), or problems that could be considered evidentiary, such as outcome measures or inclusion/exclusion criteria (to be explored further in Chapter 7). There is, however,

very little literature that looks in detail at the specific problems experienced when *conducting* a cell therapy trial. Sanchez et al. (2013), who report the results of a workshop where cell therapies trialists discussed the problems they faced, is the only peer-reviewed paper in my literature review that could be considered to focus specifically on this issue. Although this was US-based and may have limited applicability to the UK context, there are policy reports (such as House of Lords, 2013 and RMEG, 2015) which do provide a UK perspective. The main issues raised in these reports are broadly similar to those identified by Sanchez et al., and generally relate to funding (in particular funding for incremental research and slow-accruing, high cost trials) and the reimbursement of excess treatment costs, which can potentially be high. Regulatory complexity and the burden of compliance are also identified as specific problem for conducting cell therapy trials, along with the time required for trial set up.

In terms of the existing literature, then, the challenges associated with 'doing' cell therapy trials primarily relate to funding and regulation. Although these findings provide a useful starting point, they fall some way short of a comprehensive consideration of how the trials process enables or impedes the translation of cell therapies. The general challenges of cell therapy translation that I discussed in Chapter 1, such as the logistics of working with cells, could potentially have a significant impact on the conduct of a trial, but there has as yet been no detailed study of this. Furthermore, the majority of the literature on cell therapy trials, and indeed on translational challenges in general, is written by or draws on submissions by cell therapy developers themselves. These accounts thus represent the experiences and priorities of specific actors in the field, rather than taking a more holistic, academically-informed approach.

There appears, then, to be an opportunity to extend our understanding of the practical challenges of cell therapies trials. STS critiques of clinical research (e.g. Brives, 2013; Petty and Heimer, 2011) emphasise the importance of looking at the day-to-day practice of trials, however there has been very little research of this type for cell therapies. Will's 2011 study is a notable exception, providing a useful vignette of a cell therapy trial in practice. Although she focuses on the process of doing

research in the NHS, rather than on the problems of cell therapy trials specifically, her work suggests that there is value in looking at the 'doing' of the trial itself in order to understand how it fits in to the bigger organisational and translational framework. This chapter follows a similar approach, by using observational data as a starting point for a detailed analysis of the challenges of cell therapy trials. From my observations of the ENABLE trial I identified four key themes relating to difficulties the team experienced: financial constraints, temporality, working with cells, and the different domains involved in the trial. I will present each of these themes in turn, firstly discussing the evidence from ENABLE, then cross-referencing with data from the interviews, and finally summarising the nature and extent of the challenge, and considering it in the context of key literature. The concluding section of the chapter then considers whether cell therapies experience consistent and distinctive challenges in clinical trials, and discusses how the trials framework shapes practice and innovation in the field.

5.1 Financial constraints

The issue that was raised most often in the ENABLE team meetings I observed, and that seemed to be of most concern to the team, was reimbursement for the cost of the therapy - the so called 'excess treatment costs' of the trial. The team were experiencing inconsistency in the reimbursement of these costs, despite the NICE guidelines stating that the treatment should be funded (albeit only if delivered as part of a clinical study). In some cases, patients had already been randomised before finding out that funding would not be available, which led the team to change the recruitment process so that the randomisation would only be done once funding for the treatment was secured. There were also instances of patients from different counties being treated in different ways, for instance a patient from Wales would only have the treatment reimbursed if they took part in the trial, whereas a patient from Scotland was in the opposite position and could only receive funding off-trial.

Reimbursement of excess treatment costs was further complicated by the fact that there was not a direct link between the funding received and the cost of each operation. During one meeting Mr. Hamilton explained that some of his

operations cost the hospital a lot less than the standard reimbursement amount, to some extent cross-subsidising operations that do not get reimbursed. The impact of this complex and inconsistent financial situation was significant. Trial participants who are randomised but not treated due to lack of funds must still be included in the analysis, thus diluting the results, and there is also a negative impact on the patients themselves, who have spent time deciding whether to participate, and may have become emotionally invested in getting the treatment only to find that they are unable to take part. There was also an impact on the management of the trial, as a significant amount of the team's time was spent dealing with these issues, and a considerable effect on morale, demonstrated by one team member stating on numerous occasions that he would rather stop doing research altogether than continue battling with the commissioning bodies. The team themselves identified reimbursement as the biggest challenge they faced, and it was clearly their most significant concern about sustainability of their research and clinical programme in the future.

Another finance-related factor that became apparent, although in a more positive way, was the impact of funding on the conduct of the trial. The clinical trial itself was funded by a charity, with additional funding provided by a research council for basic scientific research to be conducted alongside the clinical testing (which the team felt was essential in allowing them to both test the effectiveness of the treatment and understand more about how it worked). The centre hosting the trial also was part of a wider research network that was funded by a relatively long-term grant, creating some stability and allowing the team to plan for the medium term without spending all their time thinking about grant applications. This institutional structure also provided a wider programme of research that supplemented individual clinical trials. For instance, I met PhD students based in the research lab who were working on basic scientific research linked to the treatment, social scientists working on patient surveys and follow-up studies of previous trials, and a group looking at manufacturing models for delivery of the treatment to the ward.

The fact that the ENABLE site already had access to a cell manufacturing facility appeared to have been a particularly important factor that facilitated the set-

up of the trial. The lab had originally been set up using pump-priming money from the hospital trust, and therefore the site did not need to factor the cost of setting up GMP facilities into each new trial. This funding model created an infrastructure that appeared to create a platform for clinical research that bordered on the style of practice that Keating and Cambrosio (2007; 2012) describe in oncology trials, albeit on a much smaller scale. In particular, it allowed the team to sustain a pipeline of trials - some in follow-up, one currently active, and others still being planned - creating an ongoing programme of research that could continually build upon itself. This model was not without its challenges, for instance the ENABLE trial was collecting a large amount of data that would need significant resources to analyse at some point. Overall, however, it appeared to support a sustainable programme of clinical research that also added to the basic scientific knowledge-base, which, as we will see in next chapter, is likely to be an essential feature of successful cell therapy trials.

These observations from the ENABLE trial suggest that there are two important finance-related aspects of cell therapy trials: the reimbursement of excess treatment costs, and the research funding model. In order to explore these issues further, and to assess how universal they are, I will now look at the data from the interviews for each in turn.

5.1.1 Excess(ive) treatment costs

NHS excess treatment costs were raised as an issue by a number of interviewees, some of whom, like the ENABLE team, felt extremely strongly about the issue; for instance, Interview 2 complained that:

> "The bean-counting intransigence of the NHS is worse than even the home office" (INT2)

Interviewee 3, who managed a multi-site trial, also found reimbursement challenging:

> "The hardest thing about recruitment was getting the funding for the stem cell transplant itself, that was a very difficult process." (INT3)

She went on to explain that she had to provide an economic case for every patient treated, and that the way she was able to justify the treatment cost was to demonstrate the expected cost benefits to the NHS if the treatment was successful:

> "Each person you had to do an individualised request for money, and really in the end it was a financial argument which they couldn't defend against, because the potential of removing these people from the treatments that they were having to have … so you know you have a, sort of an economic argument you can put forward." (INT3)

This experience suggests that excess treatment costs might be particularly problematic for early-phase trials, where the experimental nature of the treatment might make it difficult to make an economic case based on expected benefits to the patient.

Interviewee 1 also described problems related to excess treatment costs, however his experience was slightly different because he found it more difficult to secure reimbursement for treatments in later-phase trials, which might be expected to have some benefit for the patient:

> "Our small-scale Phase 1 trials, where obviously we don't know if there's any benefit to the patient, we'd have no trouble … but our random Phase 2 study, where there is clear evidence of benefit … now we're finding it very difficult to get the treatment costs from the NHS." (INT1)

He went on to question the current funding model, where the excess treatment costs for all publicly-funded trials are met by the NHS:

> "You could argue that the research sponsor [in this case a university] should pay the treatment costs for the Phase 1 trial because it's pure research. Whereas for the Phase 2 study you could argue that the NHS should fund it because there's a clear benefit." (INT1)

He specifically identified cell therapies as a difficult area for NHS funding, because of the combination of high costs and uncertain benefits:

> "The NHS is responsible for paying for the cost of treatment in research, and that is absolutely fine as a principle, and it's certainly fine when you're looking at [for example] a trial we did which was using intermittent compression stocking … [but] when you look at early stage Phase 1 studies by academics of expensive therapies in the current climate … where actually you need to pay this treatment which might cost you know £50,000 per patient for a Phase 1 study where at the end of it we're not going to know if it works or not … it's just not tenable." (INT1)

It seems, then, that the current approach to NHS treatment costs is likely to be problematic for expensive cell therapies, and that this challenge is not necessarily limited to early-phase trials where there is little evidence that the treatment might benefit patients.

Alongside the challenges related to high excess treatment costs, some interviewees also reported similar experiences to the ENABLE trial in terms of the inconsistency and unpredictability of reimbursement decisions. For instance, Interviewee 3 found that:

> "There's no overall, that I can see, no national strategy about it all. It's having to go individually one by one by one, each time again. And the variation we would get around the country was quite large." (INT3)

This situation is exacerbated by the fact that cell therapy trials are generally sponsored by academic institutions or SMEs, neither of which tend to have the resources or expertise to negotiate the complex HTA environment, as Interviewee 17 went on to explain:

> "It's such a huge organisation, the NHS ... From our perspective as a small organisation - who do we interact with? And where do we spend our valuable resources to influence and learn?" (INT17)

These quotes demonstrate that as well as being a crucial issue in terms of adoption, an issue that is well-established in the literature, HTA and reimbursement are also significant factors in the trialling process.

Although these findings emphasise the importance of cell therapy developers engaging with questions of cost effectiveness from a very early stage, it should be noted that not all cell therapy trials appear to have problems with reimbursement. For instance, those that are funded by external organisations that have sufficient funds to meet the treatment costs do not face such problems, as Interviewee 5 found:

> "It hasn't really been an issue for me, because when you write these grants to get the money you will cost the NHS costs in there as well." (INT5)

Even for publicly-funded trials, excess treatment costs did not always appear to have been problematic; for instance, Interviewee 9 was confused about exactly what the costs had been, but was clear that they hadn't been an issue:

> "We didn't have any treatment costs. I mean, it wouldn't be expensive - ours was completely funded by research. And I always get a bit confused by treatment costs." (INT9)

It appears, then, that the reimbursement of excess treatment costs is a significant, but not universal, issue for cell therapy trials, which manifests in different ways for different trials.

5.1.2 Funding cell therapy trials

Although the ENABLE funding model appeared to work well, data from the interviews suggests that funding is a significant challenge for many other cell therapy trials. As we have seen previously, the majority are publicly-funded, and even commercial trials tend to be funded by SMEs with limited resources. This type of funding has generally been sufficient for the early-phase trials that academic institutions have traditionally been involved in; it often proves insufficient, however, for late-stage, highly-regulated CTIMPs, which have more usually been funded by the deep pockets

of Big Pharma. A number of interviewees reported struggling to secure sufficient funding for their trials, such as Interviewee 4:

> "One of the difficulties was we applied for funding to an organisation that was known to support innovative projects … but whose grant-giving ability was … 10% probably, or maybe 20%, of what we actually needed, especially in the new terrain." (INT4)

This quote highlights the difficulty of securing sufficient funding for a large clinical trial, and also highlights the impact of the new regulations governing clinical trials in general, as well as ATMPs specifically, which have made it increasingly more expensive to run cell therapy trials.

It appears that these changes in regulations took some trialists unawares, which was another factor that could lead to the funding secured being insufficient to run the trial, as experienced by Interviewee 9:

> "Our first trial came from [charity], and it was very underfunded because again, when I put the grant in there was no regulatory hurdles at all, so it wasn't factored in." (INT9)

This quote highlights the difficulties that can be caused by uncertain regulatory environments, and uncertainty can also make it difficult to maintain a sustainable research infrastructure to support clinical trials, as exemplified by this quote from Interviewee 13:

> "We have an outfit at the moment that costs £300,000 a year run, and we have at the moment one year's funding, less - we are funded at the moment until January next year at which point we will disappear if we're not funded any further." (INT13)

The combination of funding being both limited and uncertain thus appears to create a particularly challenging environment for undertaking clinical trials.

Another factor that can complicate the funding situation for cell therapies is the expectations of funders, which may be out of step with the realities and necessities of the trial itself. One such necessity is the importance of basic science

being included in a cell therapy trial, which would not usually be expected in a translational grant, as Interviewee 16 explained:

> "I went to talk to the Wellcome Trust, and initially they said if it's a translational grant we don't want too much basic research in it. So that means you have to have a funder who's happy to give you the money for the basic science knowing that there might be someone else giving you funding for the translational, and vice versa." (INT16)

The expectations of translational grant-giving bodies are also problematic for treatments that still require significant scientific research, because applicants must promise enough to justify the costs of the study but avoid raising expectations that will be impossible to meet, as Interviewee 16 went on to explain:

> "We need more basic science, and that's one of the things that I don't find it easy at the moment, because a lot of the funders want you to apply for translational funding, but translational means you have to go into humans and I don't think that we quite have the processes to go into humans on a larger scale … managing the expectations of funders is not easy either, because if you are not ready to make ambitious claims the next group along would be and they would be taking the risk." (INT16)

Other interviewees raised further issues relating to the expectations of funders; for instance, Interviewee 5 experienced problems relating to intellectual property because the trust where the treatment had been developed had not had a commercial strategy, and had therefore not attempted to secure a patent:

> "If you go to Pharma or to venture looking for money to fund a clinical trial and you have no intellectual property, you have no patent, they're going to show you where the door is because there is no point - the conversation ends there immediately. So we could not get any money for this trial for a long time. Eventually I managed to get some money out of a philanthropist, so he is

> literally funding this out of the kindness of his heart. He's not trying to make money out of this, because he knows there's no IP." (INT5)

It seems, then, that it is not only difficult to secure sufficient funding for cell therapy trials, but that the expectations and requirements of funding bodies are sometimes out of step with the realities of the trials that need funding.

Another factor related to funder expectations that was raised by the interviewees was the fact that the milestones agreed in the grant are often unrealistic for cell therapy trials, which, as we will see in the following section, are often subject to significant and unpredictable delays. For instance, Interviewee 5 went on to explain the financial effect of a delay in getting MHRA approval for the GMP lab to be used for the trial:

> "Because it wasn't licensed we could not submit our clinical trial application to MHRA, therefore I couldn't meet that milestone, therefore this philanthropist did not pay his bill, therefore I had a debt of about £130,000 around my neck, which didn't make me Mr. Popular in the college." (INT5)

This kind of pressure from funders can happen even when the funding is specifically intended to support the set-up of cell therapy trial infrastructure rather than the trial itself, as Interviewee 9, who was funded by a *"sort of pump priming type initiative"* explained:

> "They're starting to hassle me saying "we gave you this money last January, where's the outcomes?" And we're still writing the regulatory [application], because it did require quite a lot of *in vitro* work." (INT9)

These quotes suggest that the challenge of meeting funders' expectations does not necessarily disappear once the funding for a trial is secured, but can potentially be an issue throughout the trial.

5.1.3 Summary

The funding model for cell therapy trials, and the extent to which funders' expectations are aligned with the realities of conducting a trial, appear to be problematic for three main reasons. Firstly, it is questionable whether public funding can be sufficient for the types of trial that are required for cell therapy research, which links back to the issue of academic versus commercial development discussed in the previous two chapters. Secondly, the need to fund both the scientific and clinical work required to develop the product appears to go against the traditional expectations of 'translational' work, which is an issue I will explore in more depth in Chapter 6. Thirdly, and perhaps most importantly, there is the question of whether trial funders have realistic expectations of cell therapy trials, and in particular the time it will take for these trials to be undertaken (which is one of the temporal factors that we will be discussing in the next section). Underpinning this is the issue of funders' expectations more generally, and the need to balance the promises needed to secure funding with setting realistic expectations for the trial.

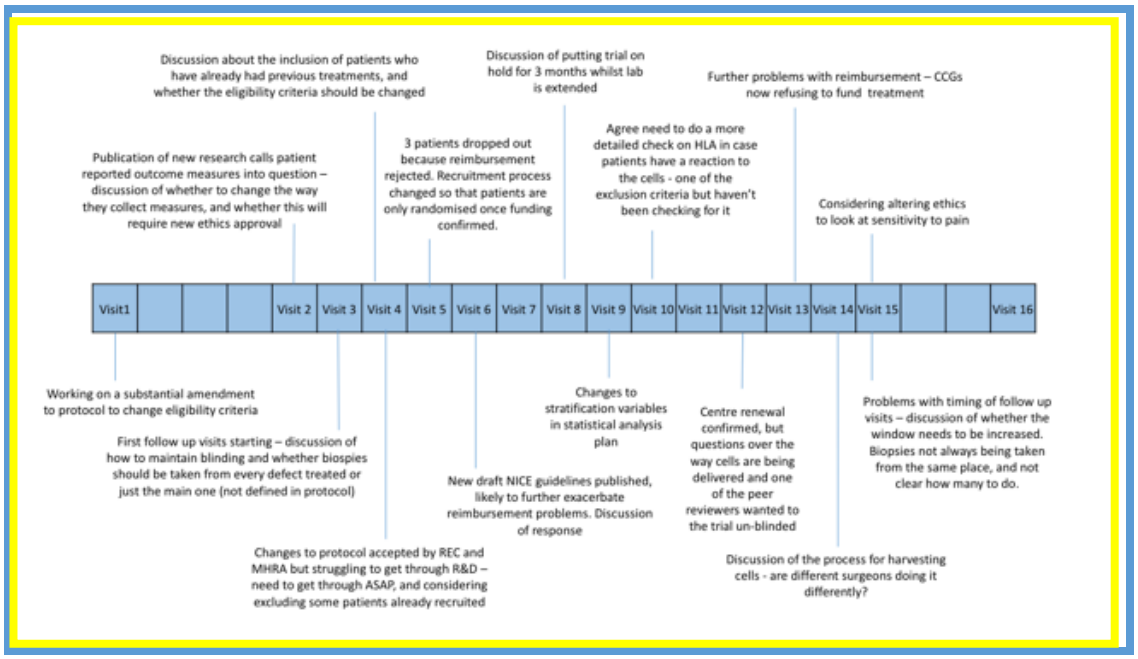
Reimbursement of excess treatment costs also has significant implications for many cell therapy trials, and again this is specifically an issue for academic-led research. As with the funding for the trial itself, securing reimbursement often requires making claims about the likely benefits of a treatment - i.e. that it offers the possibility of significant cost savings for the NHS. For early-phase trials in particular this will often be at odds with the experimental nature of the treatment, and could even be considered to challenge the premise of clinical equipoise that forms the justification for the trial itself. Likewise, raising such expectations risks adding to the therapeutic misconception that patients may have about the likely benefits of participating in the trial, which is already likely to be raised because of the hype surrounding stem cell research. It is important to note, however, that this issue is not unique to cell therapy trials: excess treatment costs are recognised as a significant problem for many trials taking place in the NHS, and the new HRA approvals process attempts to address this by considering treatment costs much earlier in the trial approval process (HRA, 2016). The scale of the problem, however, is likely to be greatest for innovative biomedical treatments such as cell therapies, that combine

high treatment costs with uncertainty about outcomes. Indeed, the issue of reimbursement is recognised as being one of the main obstacles for the translation of cell therapies, even once they are licensed (House of Lords, 2013). The appropriateness of the existing technology appraisal methods for assessing cell therapies was evaluated in a 'mock appraisal' (RMEG, 2015), however this only addresses what could be considered the adoption part of the translational pipeline, whereas my findings suggest that reimbursement can become an obstacle to translation much earlier in the process. This is just one example of how the temporality of the trial is in itself a challenge to the innovation process, which is the next theme I will discuss.

5.2 The temporality of the trial

One of the benefits of my longitudinal fieldwork with the ENABLE team was that it allowed me to observe how the trial developed and evolved over time. Figure 5.1 (overleaf) shows just some of the different factors that emerged over the course of my observations. Issues were often raised at a certain point and then faded away over time, sometimes because they were resolved, but often simply through being overtaken by other events, or by being 'tabled' as too difficult to resolve, to be returned to at a later date. It is immediately apparent from this that a clinical trial is not a fixed entity from the start, continuing to adhere to a protocol that is set in stone and never changes. Instead, it might be adapted for any number of reasons, which can be trial-related, such as realising the follow-up appointment window is not realistic, site-related, such as the discussions about closing the lab, or externally-triggered, such as taking account of new reimbursement guidelines. All of these emerging issues have the potential to change the trial itself, the environment in which it takes place and/or the environment in which the results will be used and assessed.

Figure 5.1: Issues discussed at team meetings during fieldwork period



The longer I spent observing the trial the more out of step it seemed with the 'immutable' rhetoric I associated with RCTs. Rather, this ebb and flow of micro and macro factors created a fluid and contingent dynamic that I began to think of as the temporality of the trial, and this temporality appeared to be both caused by, and create, specific challenges for cell therapy trials. One of the most notable aspects of this trial temporality was the sheer time it took to undertake the trial, which was something Amy highlighted when she gave a presentation about the site's experience of trials (Field notes 23/19/15). The process of getting approval to start the trial had taken a number of years, partly due to the change in regulations in 2007, and once approval was received there were further delays caused by issues such as having to find an appropriately qualified QP, which took over a year (Field notes 21/11/13). There were also delays once the trial was underway; for instance, it was difficult to schedule MRI scans within the windows required for the protocol, and recruitment was slower than expected at first because key team members were on holiday. The length of the outcome measure was also a significant temporal factor, because although the primary outcome was only 12 months, long-term follow up was also deemed to be important in proving the treatment superior to existing options, meaning it could be as long as 20 years before the full picture was understood.

I also noted an element of path dependency in the trial temporality; for instance, the choice of outcome measures was fixed once the trial has started, even though information became available during the trial that might make some of the measures used obsolete (Field notes 18/12/14). This issue can even continue into future trials, as Amy explained that some of the outcome measures they were using were not felt to be useful in themselves, and were only being collected to allow comparisons to previous trials. Path dependency also became an issue during peer review of the centre's funding, because new research that had been published after the trial began suggested that a different delivery method for the treatment might be beneficial. This led to one of the reviewers insisting that the team should change their treatment protocol, however it was not possible to do this for the ongoing trial, and the team were even concerned about doing so for future trials as it might invalidate the efficacy results already collected (Field notes 19/11/15).

Perhaps in response to the length of the trial and the path dependency issue, I witnessed numerous examples of the team attempting to 'future proof' their work to prevent further delays or setbacks. For instance, Mark (the cell manufacturing manager) explained that when first setting up the lab over 15 years ago, he deliberately worked to pharmaceutical standards in anticipation of a tightening of the regulations around cell therapies. This meant that when the new ATMP regulations were introduced the ENABLE team were able to continue their trials without significant interruption (Field notes 06/11/14). There were also a number of discussions about the amount of cell characterisation that should be undertaken, with some team members arguing that even if regulators don't require precise characterisation of the cells at present, they should be doing it anyway as it will inevitably become a requirement in the future (Field notes 26/11/13).

From these observations I concluded that various aspects of trial temporality were challenging for the ENABLE trial team, although many of these issues were very specific to the particular treatment, trial protocol and trial site. In the following section I will explore this issue of trial temporality more broadly, discussing how it is perceived amongst other cell therapy developers, the challenges it poses, and the various ways that trialists attempt to address these challenges.

5.2.1 Time and tribulation: temporality issues for cell therapy trials

On my very first day of fieldwork I attended a conference for cell therapy developers, and one of the speakers made a point that stayed with me throughout my fieldwork and proved remarkably insightful. He said that he regularly heard 15 years given as an approximate timeframe for a particular therapy or breakthrough to reach the clinic, both in the media and from researchers involved in the translation of cell therapies. He noted that this timeframe had been given for the past 10-15 years, and although he couldn't see that many of the treatments it had been applied to were much closer to the clinic than they had been then, he keeps hearing it repeated. This is something I noticed during my fieldwork as well, as more than once I heard 10-15 years being given as an estimate of the time it would take for a new development to reach the clinic, even in reference to a discovery in the lab that did not yet even have an obvious clinical use. It does not take a detailed knowledge of the specific cell therapy or clinical area to know that this is unlikely to be a realistic estimate - as another researcher noted, it generally takes 10-12 years for a pharmaceutical company to get a drug from bench to clinic, and cells should be expected to take much longer given the experimental nature of the research (Field notes 01/05/14). And yet the claim persists, which, particularly in the context of my observations from the ENABLE trial, warrants some exploration.

Overly-optimistic projections for getting cell therapies 'into the clinic' may be partly due to different interpretations of the term 'clinic'. If it is interpreted as 'first time the treatment is used in a human' (i.e. first in man clinical trials) then 10-15 years is not unrealistic - for instance, the first trials using iPSCs were authorised less than 10 years after their discovery was first published (Cyranoski, 2014). Furthermore, as we saw in the previous section, there is also a strong motivation to make claims for a treatment that include an imminent translation into a usable clinical treatment. From the interviews, however, it became apparent that some trialists may also be genuinely unaware of how long clinical trials take; to take one of many examples, Interviewee 9, who had just completed his trial when I interviewed him in 2015, said:

> "The grant that we've just finished was a two-year grant, which was awarded in 2007. So you can work out how much longer it's taken us to get there." (INT9)

The trial had therefore taken six years longer than originally anticipated when the grant was submitted, and it is not just the overall length of the trial that is often greater than expected, but also the time (in person hours) required to run the trial. This point was made by a clinician speaking at a regenerative medicine trials course, who emphasised the point that if clinicians wanted to get involved in a trial they should be aware of how much time it would take, even if they were not actually running it (Field notes 01/05/14). Thus, it appears that many cell therapy trialists underestimate both the length of time the trial will take to complete and the amount of time they will need to commit to working on it.

Cell therapy developers underestimating the time it will take to complete the trials process can partly be explained by a lack of awareness of how long clinical trials generally take, given that the people involved in these trials have often not worked on trials before, and particularly not on CTIMPs. However, there are also factors which can make cell therapy trials in particular take longer than expected. The most pressing issue for many of my interviewees was that the regulations changed as they were planning or setting up the trial. This meant that not only were they having to negotiate unfamiliar terrain, but also that terrain kept changing, as in this example from Interviewee 3:

> "One of the hardest things has been the fact, because it's such a long-standing trial, I think back to probably the first meetings they ever had about it, that must have been, seriously I think 2003, 2004 … And the kind of administrative, sort of the approval process has changed several times in that time." (INT3)

Interestingly, the therapy being trialled in this case was not classified as an ATMP, so was not subject to the new European regulations, however it was affected by the new clinical trials regulations. In another example, a clinician explained that when the ATMP regulations were introduced in 2007 his trial was already ongoing. Because the treatment was now classified as an ATMP the trial had to stop to build GMP

facilities and get approval, delaying recruitment by seven years (Field notes 01/05/15). Interviewee 7 described the way that regulatory changes can interact with trial temporalities to create a particularly challenging environment:

> "One of the problems with these trials and these grants is that the time-lag between submitting the grant, getting started and getting to the point of a clinical trial is often several years, by which time, especially in this area of biotechnology … the rules keep changing." (INT7)

This quote highlights the way that changing regulations can create a positive feedback loop, whereby delays in getting approval mean that by the time the trial is ready to start the regulatory landscape has changed again, potentially further delaying the start of the trial.

In addition to the delays caused by new and changing regulations, my fieldwork also highlighted numerous examples of other factors that can delay a cell therapy trial. Many of these related to the cell manufacturing; for instance, a clinician involved in one of the first trials of hESCs in the UK described how they had to change manufacturer because the company went bankrupt, and it took 18-24 months to get another site accredited, resulting in lower recruitment than originally planned (Field notes 01/05/14). In another example, Interviewee 5 described missing a funding milestone because of delays getting MHRA approval for the cell manufacturing facility:

> "We came up to milestone number three, and milestone number three was you will treat your first patient. And what scuppered us there was that our new GMP facility was not ready, it was not licensed by the MHRA as a place where you can manufacture a cell product." (INT5)

Other aspects of the procedure can also cause problems, as Interviewee 2 described:

> "[The trial] got stopped a week before the surgery with the realisation … that the injection implement that the surgeons were using, which is a simple stainless-steel cannula that had been

> produced in medical grade clean rooms in Sweden … hadn't been produced and risk assessed within a UK kite-marked stamped facility." (INT2)

In other cases it can be the science itself that delays the development of the treatment, as described by Interviewee 16:

> "We need more basic science, we need to know what is going to change these cells so we can produce the right end product as it were. And the problem now is that we clearly have the right sort of basic biology package in the grant to answer these questions, but that will take more time, which means that we can't start the first-in-man study within the remit of the period." (INT16)

It seems, then, that cell therapy trials are particularly susceptible to delays for a variety of reasons, and the positive feedback means the cumulative impact of these delays can be significant.

Trial delays can create problems with funding, as I highlighted in the previous section of this chapter, and they can also mean that some of the planned work never gets done at all. For instance, the trial that Interviewee 7 was involved in was intended to be a precursor to a second, more comprehensive study. However, because the first trial had not even started by the time the funding came to an end, the second study had to be abandoned. In other similar instances the work of the trial continued but the costs had to be absorbed by the research department, as was the case for Interviewee 9:

> "At the end of the day we did what we had to do. It took about three extra years which were unfunded, so it all became very expensive, but we got there, we were determined to get there." (INT9)

Even if the trial continues, there can be other problems caused by a delayed start, not least the logistical issues created by an uncertain start date and work load, as described by Interviewee 5:

> "The people were all trained, they came off the end of their contract so now we have to retrain them. This is the thing, there is a momentum with these things and if you lose momentum it puts you back." (INT5)

Susceptibility to delays, then, puts cell therapy trials under significant financial and practical pressures, and means that some may not be completed or might never even start in the first place.

As well as causing logistical and funding issues, the fact that cell therapy trials are so time-consuming clearly exacerbates the path dependency issue I observed on the ENABLE trial. Once the trial starts, any significant changes could mean going back to the beginning of the already long (and arduous) process, and I observed this cause problems numerous times during my fieldwork. For instance, a prominent clinician involved in one of the most advanced areas of clinical stem cell research explained that he would like to change the process that they use to produce the cells. This would have set the trialling process back five or six years, however, and he did not have the time or the money to be able to absorb this delay (Field notes 01/10/14). Examples such as this suggest there is a perception that once you start clinical trials you are essentially 'locked in' to the product as defined in the original Investigational Medicinal Product Dossier (IMPD). This feeling was articulated by another trialist, who explained to other clinicians thinking of embarking on cell therapy trials that you have to stop innovating at the point of clinical trailing, because it's very difficult to change anything to do with the product once you've done Phase 1 (Field notes 01/05/14).

This issue of path dependency is complicated by the fact that many trialists were not clear how much they would be able to change without needing to go back to the beginning of the process; for instance, Interviewee 17 said:

> "After our four patients we might realise that we have to change something quite significantly in the product, and then it's a different product. Does that mean we start from scratch, that the data from those four patients is no longer front-line data for us?" (INT17)

In another example, Interviewee 9 discussed possible changes that could be made to the procedure for delivering the cells, which would benefit patients but could be considered a significant change:

> "What we did last time was we took fluid from the patient's joint and that's what we loaded the cells with. So that was an extra invasive procedure, we actually injected the cells into the joint - for very good reasons, and I think that was the right decision at that stage. But it may be that next time we want to give them under the skin, which is less invasive. So there's all these things we want to change, which I suspect means we'd have to do another Phase 1 trial … I think that's a big question for the regulators – how much can you change and keep the product the same?" (INT9)

The issue of path dependency is clearly not a straightforward one then, with investigators expecting to be locked in to some extent once the trialling process starts, but unclear on exactly what this means.

The future proofing strategies that I observed on the ENABLE trial were in large part an attempt to address these linked issues of path dependency and uncertainty. A number of interviewees described adopting similar approaches, for instance by 'reverse engineering' their cell production process to ensure they embarked on trials with the final product in mind. Interviewee 14's experience is a good example of this sort of approach:

> "The issue with a lot of the translational engineering work is in most people's eyes it tends to be towards the end of the process, so people assume you prove it works and then you scale it up … But one of the problems there is that the regulatory pathways, they're not particularly adaptable at that point, so often you need to have planned your manufacturing whilst proving it works." (INT14)

In other cases, these attempts at future proofing related to the regulatory path, rather than the cell processing. This is exemplified by Interviewee 9, who explained

that he could have used HE for his treatment, but that he decided to secure an IMP licence instead in order to give him more options in the future:

> "We were thinking that this is a potential long-term, you know if we thought we were going to progress this therapy and we hadn't gone through the regulatory process then we couldn't do it, so we were kind of burning bridges." (INT9)

Here, then, is another example of the need to engage with issues that will affect the eventual adoption of the therapy right at the start of the trials process.

Another means of future proofing trials is to make the protocol as vague or as flexible as possible, in order to create room for manoeuvre later in the process. This approach was recommended by a cell manufacturing consultant who explained during a conference presentation that *"you shoot yourself in the foot if you state too much about how something should work in the IMPD, because then you're locked in"* (Field notes 01/10/13). Interviewee 5 gave a good explanation of how this type of flexibility works in practice:

> "It seems to me that the art of writing an IMPD is being as vague as you possibly can be … if you can get away with it: 'We will take some cells, we will put the cells in a bag, we will activate the cells, we will mix them with a virus, we will grow them with a drug and we will treat our patient.' I haven't told you which bag, I haven't told you which activating - do you see what I'm saying?" (INT5)

By introducing flexibility into a largely rigid process, then, trialists are attempting to avoid being locked into a particular version of a product or process, thus enabling them to overcome some of the temporal challenges they experience.

5.2.2 Summary

These findings suggest that the temporality of the clinical trial is a significant challenge for the translation of cell therapies, largely because of the sheer time it takes to set up and run a trial, and the resulting positive feedback loop which can cause further delays. There are regulatory changes in progress which are intended to

speed up the approval process and reduce the administrative burden, for instance the new trials approval process in the UK (HRA, 2016), and the changes to the EU Clinical Trials Directive (NHS European Office, 2014). However, these changes to the overall trial process, even if successful, will not necessarily address the majority of the delays reported by my interviewees. Many of these delays were specific to the cell therapy itself, and were often either unpredictable and/or unavoidable. It seems, then, that both funders and trialists would do well to adjust their expectations of how long cell therapy trials are likely to take, and to ensure that time and funds are allocated to allow for unexpected delays.

The time required to undertake trials has clearly been unexpected for many cell therapy developers, who are often unfamiliar with the trialling process. This suggests there is a need for more expert advice for those embarking on trials, specifically for those working in the academic sphere who are unused to CTIMPs. Trial temporality is also problematic for innovation because to some extent trialists are locked in once the process has started, so that not only do the trials take a long time, but once they start it is very difficult to change course. This is a particular problem in this field because of fast-paced changes in the science, meaning that the clinical results could well be irrelevant by the time the trial finishes. This raises the question of whether the linear trials approach, which was developed for drug development, is practical or appropriate in such fast-paced biomedical fields. I will explore this issue in more depth in Chapter 6, which investigates the interconnected scientific and clinical uncertainties that are at the heart of cell therapy innovation.

As well as the practical implications of trial temporality, it is also important to understand the actions trialists take to overcome temporal challenges. We have seen that some trialists are attempting to future proof their trials by anticipating what regulators will require in the future, for instance in terms of cell characterisation or production requirements. These findings suggest that Faulkner's concept of 'governation' applies not only to existing regulations, but also to the expectation of future regulations - what we might term 'anticipatory governation'. What is particularly interesting here is that existing regulations may be complex and inconsistent, but they are at least certain and fixed, at least at any given point in time.

In contrast, however, there can be many different views on what future regulations might be, and therefore many different opinions on how best to anticipate them. This can lead to conflict or negotiation amongst research teams, for instance the disagreement in the ENABLE network about the importance of cell characterisation. It can also result in different sites adopting very different approaches; for instance, the ENABLE site pre-empted the ATMP regulations by setting up GMP-compliant facilities before they were needed, whereas Interviewee 2 reported having to start again from scratch. Another way that trialists attempt to future proof their work is by building flexibility into the trial, allowing them to address the path dependency issue to some extent. This too increases the provisionality of the trial, moving it even further away from the immutable ideal of EBM rhetoric. This provisionality is necessitated, and increased, by the complex and unpredictable nature of the cells themselves, which is the next theme that I will discuss.

5.3 Working with unruly cells

The third theme I identified during my ENABLE fieldwork was the challenge of using cells, a living organism, as an investigational medicinal product (IMP). In comparison to the issues of reimbursement and temporality, members of the ENABLE team themselves did not necessarily identify working with cells as a particular problem. This was no doubt partly because most of them had been working in this area for a long time and were therefore very experienced in using the cells, and also because the site has its own dedicated GMP facility. Despite this, however, my own observations identified a number of challenges raised by the use of cells. Most predominantly, the fact that cells are living organisms means that the process of manufacturing a cell therapy is less predictable and controllable than manufacturing a drug. This created specific problems with adhering to a rigid trial protocol, as exemplified by an incident that was discussed in one of the team meetings I observed. A patient had been randomised to a treatment arm that required two different types of autologous cells to be produced, but only one cell type had grown adequately in the lab. The team was faced with a dilemma: should the patient be treated with only the cells that had grown - which would be an appropriate

treatment, but would break the randomisation and therefore be a protocol violation - or should there be a second attempt to grow the required cells, which would involve an additional invasive procedure for the patient and would not necessarily be successful. Here we can see that the needs of the research, in this case the allocation of the patient to a specific treatment arm, came into conflict with the clinical care of the patient because of the logistical requirements of cell therapy production. Interestingly, it was clear from the discussion that the patient's clinical needs were given priority, with the impact on the research only being considered as a secondary factor.

The second issue that arose from working with cells was the importance of having access to GMP-grade facilities. As noted earlier in the chapter, this allowed trials to continue uninterrupted when the ATMP regulations were introduced. Mark explained to me that when they had attempted to run multi-site trials, which involved sending cells from their lab to other clinical locations, they had encountered problems with the receipt and handling of the cells at other sites. Consequently they now preferred to use their own cells at their site only, where they could control the whole process, and were encouraging other centres to set up their own manufacturing facilities using the same model. Clearly, then, the availability of an experienced manufacturing centre was an important factor in the success of the ENABLE trial. However, there were still manufacturing challenges to be overcome, with one of the most important being the issue of capacity. This was particularly acute because the ENABLE lab uses an open system for cell processing, which is more labour-intensive than a closed system. Additionally, as Mark explained, his expertise and experience were important factors in the successful processing of the cells, because over the years he had developed a 'feel' for which cell batches would grow well (Field notes 06/11/14). The importance of this tacit knowledge would appear to be problematic for a clinical trial, which requires strict adherence to a protocol. It also creates logistical issues in terms of capacity, which were apparent in the team's discussions about scheduling recruitment to make best use of lab availability.

Although manufacturing capacity was clearly an important issue, the team were not all convinced that this was the most important factor that limited

recruitment. There was much debate in team meetings about whether other factors (such as access to the operating theatre, the availability of surgeons, and MRI scanning slots) were in fact more of an issue than the availability of cells. Clearly, however, the needs of the trial were at times in conflict with the manufacturing process. This was emphasised by the fact that although there was a budget available to extend the lab, thus increasing capacity, the team were reluctant to do this because it would mean the lab being out of action for a few months and trial recruitment would be significantly delayed. My ENABLE fieldwork, then, identified the uncertainty of manufacturing cell therapies as an important challenge for clinical trials. The issue of cell therapies being living organisms, and production therefore being less predictable than drugs, is well-established in literature on translational challenges for cell therapies (see discussion in Chapter 1). What is most relevant to explore in the interview data, therefore, is how these challenges manifest specifically in the trials context - i.e. when the treatment is being produced as an IMP, and is subject to the rigid requirements of a clinical trial protocol.

5.3.1 Cell manufacturing and the clinical trial

The issue of cell manufacturing for trials was raised by the majority of interviewees, many of whom described having to account for this when planning the trial and developing the protocol. For instance, Interviewee 1 explained that:

> "It's a Phase 3 study of cell therapy vs. an antibody therapy, so it has to take account of the fact that some of the patients will fail to get cells produced." (INT1)

As this quote highlights, using cells as an IMP was generally considered to be most problematic for autologous treatments, where there is greater uncertainty in production because the cells are taken from the patient and grown on a case-by-case basis. Sometimes the underlying illness also made the resulting cell product less effective, as Interviewee 5 explained:

> "When you do research in the lab and you take blood from 20 something PhD students, you put your retrovirus on the T-cells and you get a 70% efficiency of gene transfer, you can do a nice

> experiment. But of course it's not real life, because you're dealing with patients who are sick, whose T-cells don't grow very well, so you may end up with a gene transfer efficiency of say 5%." (INT5)

This uncertainty is likely to be particularly problematic in the context of a rigid trial protocol, because for many treatments it will be impossible to produce an identical product for each participant.

As well as inherent differences in the initial cell population, producing a cell therapy can also be unpredictable because of factors related to the manufacturing process, as this quote from Interviewee 7 demonstrates:

> "When you change the reagents we discovered that the yield of [cell type] cells was much less than it was in the past." (INT7)

Complexities such as these mean that it is important that the individual working with cells have the appropriate expertise, such as the tacit knowledge that Mark described having built up during his years producing cells at the ENABLE site. Interestingly, on-site expertise in cell processing can be important even for allogeneic treatments that are mass-produced centrally and distributed to treatment sites, as this quote from Interviewee 11 demonstrates:

> "Why we need the cell labs for the trial is because they need to thaw multiple bags, they need to pool them together make sure there's the right cell number and things like that. And so right now it's not as simple as just going to a pharmacy and getting a biologic out of the freezer." (INT11)

Cell manufacturing expertise, including tacit knowledge built up over time, thus appears to be an important enabling factor for cell therapy trials, and again this does not align well with the rigid expectations of a trial protocol.

These findings suggest that the unpredictability of manufacturing cell therapies presents a significant challenge for clinical trials. However, it is important to note that although uncertainty in cell production was mentioned as a challenge by the majority of interviewees, not all trials had problems with this. For instance, although Interviewee 6 (who manufactured an allogeneic MSC product) described

variability in the numbers of cells produced from each donor, she said this didn't create a problem because there was a steady stream of donors so she was always able to produce enough cells for treatment. There were also some examples of autologous treatments that were relatively straightforward to produce; for instance, Interviewee 9 said:

> "I think heterogeneity of our product is probably less than some of the other products that you're hearing about, just because of the way that we manufacture the cells they are pretty pure." (INT9)

It appears, therefore, that although working with a cell product often creates significant uncertainty for clinical trials, this is not necessarily true for all cell therapies, and is not always problematic when it does occur.

As I observed on the ENABLE trial, the rigidity of a trial protocol can be problematic for trials where producing a consistent product is difficult. A number of interviewees described their concerns about not being able to treat patients who might have had their hopes raised, and even been subjected to an invasive harvesting procedure, only for the cells to fail to grow. In the words of Interviewee 5:

> "It would be a disaster to have a situation where you recruit a patient … and you can't give them a cell product, that would just make everybody feel lousy, you know. So it's all about trying to prevent that scenario from happening as best you possibly can." (INT5)

Although this variability is of course an issue in all instances where cells are used in the clinic, it is specifically seen as a challenge in the context of a clinical trial, where the rigidity of the protocol leaves little scope to use clinical judgement. This can be seen in an example from Interviewee 12, who explained that because of the need for an exact product specification in the protocol, he could be faced with the issue that a product might be functionally acceptable but not quite meet the cut off for use in the trial:

> "So now we make it and it's 49% - OK, what do we do in that setting? The clinical trial product specification is 51% or more ... do

> we not treat that patient, do we treat that patient off-trial, because it's not the product specification you've met. But you made it legally as an investigational medicinal product, so you can't give it to the patient [off-trial] because it was made as an IMP." (INT12)

He went on to explain that he had circumvented this issue by producing the cells under two different licences, allowing patients to be treated either on-trial or off-trial, depending on how well the cells grew:

> "The way we've got around that - and this is dancing on the head of a pin … when we're setting up that sort trial we set up a situation where the physician also requests the product as an unlicensed medicine to be used and therefore … because I've got both licences we manufacture it under both processes and then release it depending upon, so if it doesn't meet IMP product specification I'll release it as an unlicensed medicine and then the patient can be treated against that prescription." (INT12)

Here, then, we can see yet another example of trialists building flexibility into the trials process to give themselves room to manoeuvre.

The importance of flexibility was noted by Interviewee 1, who experienced problems in one of the first trials he ran because the protocol was too specific about the product specification. He reflected that:

> "I suppose that's an example of where you should be careful of how you write trial protocols." (INT1)

Intentionally making product specifications vague was something that many interviewees reported, for instance Interviewee 5 described the release criteria being intentionally broad in order to account for uncertain cell production:

> "One of the philosophies I have had in designing the trial has been to make things as flexible as you possibly can to build in safety measures. So all of the dose levels have a range, so if we don't hit our target, we'll hopefully be at the lower end. And you know

> something, if we don't even hit that we'll enrol the patient in the cohort below." (INT5)

The use of the word 'safety' here is interesting, as it does not in this case refer to the safety of the product itself - i.e. the risk of being treated. Rather, it reflects the level of concern many interviewees showed for protecting the patient against the risk of *not* being treated. Just as I saw in the ENABLE trial, most of the interviewees appeared to prioritise clinical care over the needs of the research (in this case for a precisely-defined product). This protective stance towards the patient is exemplified in this quote from Interviewee 9:

> "We intentionally made all of our release criteria relatively lax to make sure that we can give them every time, partly because the patient has gone through such a lot by the time they get there." (INT9)

Thus, in addition to the future proofing flexibility described in the previous section, which was intended to protect the research and product development, flexibility is also being introduced as a means of protecting the patient's clinical needs.

Trialists clearly expend a significant amount of effort to protect both the research and the patient against the rigidity of a clinical trial. This endeavour is particularly challenging in the context of manufacturing clinical-grade (i.e. GMP-compliant) cells. As I observed at the ENABLE site, the availability of a dedicated GMP facility meant that the team did not experience significant problems manufacturing clinical-grade cells for the trial. Some interviewees also had access to dedicated manufacturing labs, and they too generally did not find GMP production difficult. Some in fact often spoke in very positive terms about their facilities, as in this quote from Interviewee 5:

> "The trial is going to be run in our clinical research facility here … within the middle of the clinical research facility we have a GMP facility where we can manufacture cell products. It's absolutely beautiful up there, it really is." (INT5)

Dedicated GMP facilities can support the development of a portfolio of trials within a particular clinical research centre, as was the case for Interviewee 1. It can also facilitate the receipt of cell therapy products manufactured elsewhere, as explained by Interviewee 12:

> "The reason why we're doing so many commercial trials is because my lab is a pharmacy - so the chief pharmacist will say 'it's one of those, [Interviewee 12's] team will look after it.' We'll then receive it in our unit, we don't even ask the pharmacist, we take over taking it to the wards, thawing it, delivering it to the PI." (INT12)

The importance of trial sites having access to GMP facilities is emphasised by the experience of Interviewee 10, who described the difficulties experienced at sites that did not have such facilities:

> "What it involved is taking the … investigational product, the ATMP, and defrosting it and counting the cells. So this is very straightforward but it requires a certain … level of, type of, laboratory and a trained person. And essentially the NHS was incapable of providing that … the only labs that could do this were university labs, and they were extortionately expensive because they would do full economic costing on everything … The UK was more expensive than the US sites." (INT10)

The availability of an appropriate, and affordable, cell processing facility therefore appears to be an important factor for all sites involved in cell therapy trials, regardless of whether the site is manufacturing the product or not

Interviewee 10's experience also highlights another issue with the availability of labs for cell therapy trials, which is that the complexity of the product will often surpass the expertise of an NHS facility. As a scientist involved in developing reprogrammed cells for clinical use commented: *"Not everyone can do this. Yes, it's cookery, but it's cookery with lots of nuances"* (Field notes 01/05/14). This further highlights the importance of experience, of accumulated tacit knowledge, that I observed on the ENABLE trial - knowledge that is only likely to develop in a lab

dedicated to producing these cells, most likely in an academic context. Unfortunately, however, these labs have traditionally only produced research-grade cells, and there are significant financial and cultural obstacles to setting up GMP-compliant facilities in academic settings, as explained by Interviewee 2:

> "The money is all academic funding, is discovery science, and dominated by the need to get high impact publications. Building a facility for regulatory compliance does not generate any discovery science, it's all to do with just repeating things over and over again to validate." (INT2)

He went on to explain that his university's lack of experience of setting up such facilities was also a significant obstacle:

> "The first challenge was what the hell was actually required, because … production standards are very different to what universities, academics and trusts are used to doing. So we took the regs and adapted the clean room over a period of a couple of years, with limited resources. We were able to buy a limited amount of external advice, but the biggest single factor was university estates departments simply don't have a clue, and they did everything wrong. So by the time we tried to get our first inspections, everything had to just be stripped again, starting from scratch." (INT2)

It seems, then, that access to GMP facilities may be a limiting factor for trials, because the academic sites that have the cell manufacturing expertise are often not suited for producing clinical-grade cells, and conversely sites that are GMP-compliant may lack expertise in the cells themselves.

As well as lacking experience in GMP production, academic laboratories are also not ideal manufacturing sites for cell therapies because they are not necessarily set up to provide the level of service that is required from a clinical lab. For instance, Interviewee 11 described the problems he experienced when using an academic lab to process cells for one of the trial sites:

> "It had people with experience with stem cells and stuff, but it was more of an academic group. So they weren't just there 24/7 thinking about preparation and manipulation of cells, they were academic guys that also had their own research going on." (INT11)

An alternative to using academic labs is to use existing clinical infrastructure, such as NHS Blood Transfusion Centres or transplant facilities; for instance, when Interviewee 3 was asked if cell processing capacity was a factor in selecting sites to host the trial she replied: *"Oh yes. So they were all assigned transplant centres."* When this type of institutional support is available, the process of running a cell therapy trial can be fairly straightforward. However, the interviewees who reported using existing systems were generally working on trials using hematopoietic cells, which have a long history of clinical use, or were testing therapies that required minimal manipulation of the cells (such bone marrow aspirate). These are both very similar to existing transplant processes that hospitals are used to undertaking, and there was no evidence from the interviews to suggest that these same systems would provide a useful infrastructure for more complex or unfamiliar cell therapies.

As well as having limited expertise in novel cell therapies, existing clinical facilities can also have issues with capacity, as experienced by Interviewee 9:

> "I think the fact that the facility here tends to deal with bone marrow transplant patients and stuff like that, they just don't have the capacity." (INT9)

Lab availability is particularly problematic when it interacts with the needs of recruiting patients to the trial, as Interviewee 9 went on to explain:

> "We could only treat patients when there was a gap in their schedule, and it's just been a scheduling nightmare to be quite honest with you … They said, you know, we can only do one a month … and even sometimes you couldn't recruit a patient so you'd miss a month, or then one month they'd have a holiday so you miss another month - it just wasn't easy." (INT9)

This was also an issue for Interviewee 8, who found that despite the process working well in general, the availability of the lab occasionally affected a patient's treatment allocation:

> "The only time when there was an issue was primarily around staffing at NHSBT to be available to do what they needed to do … When things were delayed sometimes they found that if they were randomised to the active group they just didn't have the time or the resources to be able to do what they needed to do, so they ended up being crossed over." (INT8)

These examples suggest that, as with the ENABLE trial, the demands of the cell manufacturing process can often clash with the requirements of the trial.

Although these examples demonstrate that access to the cell lab can be a problem for trials of elective procedures, this is to some extent manageable by planning the treatments around the availability of the lab. For instance, Interviewee 3 explained:

> "You just wouldn't start the mobilisation. You would push back the mobilisation, wait for the right time slot in order to know that you could then, if they got randomised early then you'd be able to fit them in. So there probably was a bit of, you know, jiggling around." (INT3)

Capacity becomes much more problematic, however, when the trial is testing a treatment that has to be delivered in a particular timeframe, such as stroke or heart attack treatments that must be given within a certain length of time of the event occurring. In one example, a clinician involved in a stroke trial described how 50% of eligible patients couldn't be included in the trial because of lab availability, which had obvious implications for recruitment and cost (Field notes 19/01/2013). She also described it as very hard for the patients, with one in particular being very keen to take part and being devastated to find out they would not be able to receive the new treatment after all. Clearly, then, the availability of labs for acute treatments is

another factor that affects the research vs. care dynamic in cell therapy trials, although this will probably only affect a small proportion of cell therapies.

5.3.2 Summary

My observations of the ENABLE trial, corroborated by and interlaced with interview data, indicate that access to GMP facilities is an important factor in the successful running of cell therapy trials. Sites which had dedicated GMP labs tended not to experience significant problems with the cell manufacturing aspects of clinical trials, and indeed were often able to support a portfolio of different trials. However, it appears that there can be problems with the cost and availability of academic GMP facilities, and setting up such facilities in academic institutions can be very difficult. This aligns with the findings of Pearce at al (2014), who found that sites with experience in manufacturing cell therapy transplant products (and therefore with existing GMP facilities) were the most successful at developing ATMPs, and that sites without this experience found it difficult to enter the field, leading to a shortage in academic facilities. My findings also suggest, however, that using existing transplant facilities can be problematic for clinical trials; some interviewees found existing facilities to be adequate, whereas others reported problems with either expertise or capacity, which was particularly a problem for acute treatments. This highlights the significant variability in experience across the trials I examined, which is partly due to the variability in the trials themselves - which leads to very different cell processing requirements - and partly due to different local conditions. This suggests that there is unlikely to be a 'one-size-fits-all' model of cell manufacture that would work for all trials, but rather that there will be a number of different models that will be appropriate in different circumstances.

As well as making the set-up of trials more difficult, the logistical issues around cell manufacture can affect the conduct of the trial itself, as can the uncertainties introduced by using a living organism as an IMP. Although these issues were not present in all trials, where they did occur they led to patients being excluded from the trial, or having their treatment allocation changed, as well as to flexibility being written into the trial protocol and some patients being treated off-trial. Thus, it appears that the requirements of cell production introduce an additional

complicating variable into cell therapy trials that is not present for drugs. This creates distinctive issues in the research vs. care dynamic of the trial, and means that many trialists undertake significant 'work' or 'struggle' to protect the clinical needs of the patient within the rigid framework of the trials protocol and the wider clinical research framework.

Cell manufacturing is not an exact science, and appears, to some extent at least, to involve a certain amount of tacit knowledge, or expertise. This potentially conflicts with the mechanisation required to scale up the production of cell therapies, and is also at odds with the tenets of EBM, which aims to reduce the role of expert knowledge in favour of objective measures and reproducible evidence. The complexities and uncertainties of the cell production process also mean that the relationship between the cell manufacturer and the clinic is an important factor in the overall conduct of the trial. Again, this is very different from drug trials, where the manufacturing is completely arm's length from the clinic. This distinctive aspect of cell therapy trials is linked to the final theme that I identified in my ENABLE fieldwork, which relates to the challenges created by the number of different domains involved in cell therapy trials, and how the interactions between them affect the trial itself.

5.4 Different domains, disparate voices

One of the most noticeable things about the ENABLE trial, and indeed one of the reasons it made a good fieldwork site, was the regular team meetings that took place. These meetings were held fortnightly once the trial was open, although they had been weekly during the set-up period, and those meetings that I observed lasted on average about an hour, with some being as long as 90 minutes and others only 30. Regular attendees included the Chief Investigator (Mr. Hamilton), the head of the research lab (Claire), another member of the scientific research team (Kelly), the trial statistician (John), the trial manager (Amy), and the head of the cell manufacturing lab (Mark). This group was then occasionally joined by others, including another surgeon treating patients on the trial, a radiologist, other members of the scientific research team and the research nurse.

This attendee list indicates the breadth of different specialities and disciplines involved in the trial, which I broadly categorised into four distinct domains: clinical (including surgery, nursing and clinical support services such as radiology), cell manufacture, scientific research, and evidence-based medicine (including trial design, management and governance).[11] A fifth domain, pharmacy, was also integral to the trial in the form of the QP who was required to sign off the cell batches – however, he only visited the site once a month and generally only interacted with Mark, who then reported his views to the meeting. Given that most of the regular meeting attendees were senior staff with a lot of other demands on their time, the fact that they almost always attended these fortnightly meetings represented a significant investment of time on their part. This confused me at first, as many of the meetings appeared to deal with relatively low-level administrative issues. However, as my fieldwork progressed it became apparent that these meetings were in fact crucial to the smooth running of the trial.

One of the meetings' most important functions was to provide a regular opportunity for the different domains working on the trial to communicate, and crucially to discuss how any arising issues in one domain might impact on the others. A typical example of this was a discussion that took place about the incident when a patient's cells failed to grow, which I have described earlier in this chapter. Although on the face of it this might appear to be a manufacturing issue, it also had a knock-on effect on a number of other areas. Firstly, there was a clinical implication, because Mr. Hamilton was concerned about how the patient would be treated, and also because of the possible need to reschedule theatre and radiology slots to

[11] I use the term 'domain' here to describe the full extent of the conceptual territory encompassed by each of the different areas involved in cell therapy trials, which includes both the day-to-day work of individuals, and the academic, regulatory, institutional and conceptual frameworks underpinning that work. Other terms used in the literature do not fully reflect the variety of activities I am trying to convey. The term 'discipline', for instance, suggests to some extent a defined field of academic research, and whilst this might reflect the work undertaken by basic scientists it does not reflect the day-to-day activities of a hospital pharmacist or the complexities of the EBM framework. Likewise, the term 'profession' could be used to distinguish between the work undertaken by clinicians, pharmacists and scientific researchers, but it does not address the differences between a laboratory used for scientific research and one used for cell manufacturing, and it does not reflect the role played by non-human actors such as GMP regulations in cell manufacturing, or GCP regulations in trial governance.

accommodate a different treatment protocol. Secondly, there was a scientific implication, partly because Claire was interested in why the cells hadn't grown, but also because the team had concerns about whether the patient not being treated according to their trial allocation would affect the scientific analysis they were planning to do. Thirdly, there was an impact on the trial itself, both in terms of trial management, such as needing to reschedule follow-up visits, and in terms of trial design, because of the need to decide how this patient's results should be treated in the analysis.

During the team discussion it was clear that the members of each domain didn't necessarily understand the perspective of the others, but that they were happy to accept the view of the expert at the table. So, for instance, John explained that from a trial perspective the patient would have to be analysed according to their allocated treatment, regardless of what treatment they actually received (so called intention-to-treat analysis). Both Kelly and Mr. Hamilton expressed incredulity that this was the case, with Kelly summing up her view by saying *"it seems baffling to me."* This was clearly part of the incomprehensible 'trials' world rather than the more logical 'clinical' or 'scientific' world that they understood, but they recognised that despite being unfamiliar to them, the requirements of the trial were valid, and they were happy to accept John's expertise in this area. However, the discussion also allowed them to ensure the needs of their own domains were met. Mr. Hamilton insisted that the decision about which treatment to pursue would be made purely on a clinical basis, and that the resulting impact on the trial could only be a secondary priority, and Kelly confirmed that she would be able to analyse her scientific samples according to the actual treatment given. In this way, the discussion at the meeting allowed the team to understand the issues other domains were facing, and delegate decisions to the domains that 'owned' them whilst retaining control of their own areas.

This event was also a good example of another function of the regular meetings, which is that they helped the team to resolve conflict when the needs of different domains (or the personal views of individuals) were at odds with each other. This was particularly apparent in the ongoing discussions about two important

decisions facing the centre: firstly, the question of capacity, and specifically whether trial delays were primarily caused by bottlenecks in the lab, theatre or patient recruitment; and secondly, the question of what the long-term aims for the treatment should be, and in particular whether they would need or want to apply for a marketing authorisation at some point in the future. Each individual had strong views on these issues, which were often incompatible with each other. The meetings appeared to be an opportunity for these views to be aired, so that even if no consensus was reached the issue could be temporarily set aside and the day-to-day work of the trial could continue. It was notable that if a discussion became slightly confrontational, and the issue could not be resolved, the discussion would often move on either by someone making a joke or voicing a complaint about an external factor, often the MHRA, NHS England or the hospital administration. This appeared to relieve the tension and allow the meeting to move on, thus helping to maintain the cohesion of the team and keep the trial running relatively smoothly.

It seems, then, that these meetings were crucial to the team dynamic, improving each domain's understanding of the others and allowing conflicts to be resolved constructively, or allowing the team to move on from issues where consensus could not be reached. Part of the reason this was so important is that there were so many different domains involved. Although the clinical and trials domains are generally involved in any clinical trial, it is less usual to see manufacturing and scientific research being so heavily involved, and in fact this is one of the most distinctive features of cell therapy trials. I concluded from my observations of the ENABLE trial that the smooth interaction of all of these areas appears necessary for a cell therapy trial to run successfully (and indeed at all), regardless of more extrinsic factors such as regulation and reimbursement. It was surprising, therefore, to find that few of the other trials I encountered appeared to have such structured trial management processes in place. Nevertheless, my interviews yielded numerous examples of the different domains involved in cell therapy trials, and the importance of the interactions between them. In the following section I will explore these relationships in more detail, beginning with the crux of translational research, which is the interaction between science and the clinic.

5.4.1 Bridging the divide: (un)productive relationships between the domains

The clinic is the most visible, and perhaps the most dominant, domain involved in the day-to-day work of cell therapy trials, and a number of interviewees described it as challenging. This was largely due to clinicians needing to work outside of their usual sphere of experience, for instance by trialling a medicine as opposed to a surgical technique, as Interviewee 12 explained:

> "When I said to the surgeons … it's the use of medicines committee, they thought I was mad … They're used to getting a heart - that's completely different because it's not a medicine." (INT12)

In other instances, the trial presented challenges because of the need to coordinate clinicians working in different clinical areas, as Interviewee 3 described:

> "One of the reasons that was difficult is because we're working across specialities …we have gastroenterology patients undergoing a haematological treatment. So within each centre you have to have the gastro guys and the heamo … they have to both be behind the trial and its aims." (INT3)

She went on to explain that this was particularly challenging because it required both clinical areas to work in unfamiliar terrain:

> "These are gastro patients, so you absolutely have to have gastros on board and can see that this is worth trying on their patients, because it's a very new treatment, an untried treatment, a very risky treatment - particularly for this group of patients because they're prone to infection. And you also have to have the haematologists being behind taking on a group of patients that they actually have no experience of - they're not cancer patients, it's not a life-threatening illness." (INT3)

In addition to these issues of experience and familiarity, the clinical domain also has a distinctive culture which is not always conducive to the successful running of a trial, as highlighted by Interviewee 8:

> "Clinicians want everything yesterday generally ... it's part of their profession, in that their training is that they have to make decisions and they have to make decisions now." (INT8)

Thus, despite being the most dominant domain in trials, and often the driving force behind them, interactions with clinicians can nonetheless be a problematic aspect of cell therapy trials.

As well as being unfamiliar to many clinicians, and requiring new links between specialties, the ENABLE trial demonstrated the importance of clinicians working closely with scientists when developing and trialling cell therapies. It seems, however, that this is not always easy to achieve, and that there may be a reluctance in the clinical domain to engage with scientific research. Interviewee 7 (a clinician-scientist) felt that there was an urgent need to bridge the gap in understanding between scientists and clinicians in order to move forwards with cell therapies in his area:

> "One of the big messages I try to say to [clinicians in my area] is that … you have to talk to the basic scientists, you have to develop a common language, and you have to move forward together." (INT7)

The use of the word 'language' here is very interesting, as it implies that the barriers between the two areas are, partly at least, caused by a breakdown in communication - that they don't understand each other because they use different terminology, rather than because of any fundamental differences in approach. This language barrier is exacerbated by a lack of people who have experience of both domains, as Interviewee 7 went on to explain:

> "I'm fortunate because I did my research in cell-based therapies so I know a lot about the basic science of it, and I know the clinical side of it because that's what I do, so I understand it. But the big problem is that a lot of people aren't fortunate enough to have been exposed to both sides of it, so they're very dependent on

> what the other person is telling them. And if they don't understand each other that can be a problem." (INT7)

This quote emphasises the importance of engagement between science and the clinic, and reinforces the importance of regular communication, such as the ENABLE team meetings, for facilitating this engagement.

As well as a lack of engagement amongst clinicians, my fieldwork provided numerous examples of scientists being unfamiliar with, or actively distancing themselves from, the clinical domain. In one instance, I was observing at a conference run by a national translational network which specifically aimed to bring together clinicians and scientists working on a particular regenerative therapy, and a scientific PhD student specifically raised this issue: *"I've no idea about the surgical side"* (Field notes 21/11/13). In another instance one of the interviewees, who had been involved in the basic science behind one of the most recent 'breakthroughs' hyped in the media, specifically distanced himself from the clinical side of the research, saying:

> "I'm not a clinician - I'm a rat doctor. I'm not a doctor, well I have a medical degree, but I'm a rat doctor." (INT13)

This lack of engagement could be considered surprising given that these scientists are involved in research that has a specific clinical aim, and, as discussed earlier in this chapter, some interviewees found that research funders tended to favour grant applications that make ambitious translational claims. However, other interviewees felt that it was actually easier to secure funding for basic science (albeit with a broadly translational aim) than for clinical research. Interviewee 10 felt that this meant there was little motivation for basic scientists to engage in clinical issues:

> "The basic lab stem cell guys and girls are not interested in spending their time talking to clinicians when they're getting their big basic science grants in." (INT10)

Clinical research was also perceived by some to be a riskier career path for a basic scientist because it is unpredictable and unlikely to lead to high impact publications, as highlighted by Interviewee 9:

> "The trouble is unless we cure [disease type] … or get some really interesting biomarker [we won't get high impact publications]. I shouldn't be quite so negative, but it's tough to publish this sort of stuff." (INT9)

It seems then, that although the translational agenda would appear to encourage scientists to engage with clinical research, in practice there are funding and career considerations that may discourage them from doing so.

As well as the importance of clinicians and scientists working together closely on cell therapy trials, my interviews confirmed that a close relationship with cell manufacturers is also an important factor. Interviewee 1 had set up his own facility for manufacturing cells when the local NHSBT unit closed, and this allowed him to discuss his precise requirements with the manufacturer and have good control over the process. He was one of the few interviewees who didn't report any logistical problems with manufacturing, and notably he was also the one who reported conducting trials specifically looking at the logistics of cell manufacturer and transport, for instance looking at the effect of freezing the cells. This suggests that having a close relationship with the cell manufacturer facilitates the development of more efficient manufacturing methods, thus supporting both individual trials and the longer-term development of treatments.

Close engagement between trialists and cell manufacturers is also important because of the need for manufacturing to be compliant not only with Good Manufacturing Practice (GMP), but also with Good Clinical Practice (GCP). The difficulties this can cause are exemplified by this quote from Interviewee 12, who ran a manufacturing lab within a hospital that sponsored a variety of trials:

> "An adverse event is not just the responsibility of the sponsor to report, as a manufacturer I'm the qualified person so I have a legal responsibility for the quality of my product … So of course we have a death on trial, I contact the MHRA, they say we don't want to know. So then when GCP at the sponsor says … 'you spoke to the MHRA what do you mean you spoke to the MHRA?' - well I had to … And the fact is you've never worked for an organisation that's

> also a manufacturer, so you don't know that … it's not a case of GCP, it's a case of GMP, I had to do it." (INT12)

This quote highlights the structural difference between a traditional drug trial, where the IMP would usually be manufactured by a pharmaceutical company and delivered to the hospital, and a cell therapy trial where the IMP is being manufactured on site. This is novel terrain for investigators, sponsors and manufacturers, and good communication between them is likely to be an important factor in ensuring cell therapy trials run smoothly and are compliant with regulations.

In contrast to the clinical, scientific and manufacturing domains, which are involved in both the practical and the innovative aspects of cell therapy translation, the role of pharmacists appears to be largely a logistical one. Pharmacy can be involved in cell therapy trials in two main ways: if cells are produced off site then hospital pharmacy departments will usually be required to receive the cells, and for cells manufactured on site a QP is required to sign off batches of cells. Both of these roles are essential to the trial, because without them the IMP cannot be released and the trial cannot proceed, but they do not generally have an impact on the development of the treatment itself. Pharmacy can be understood, then, as playing an important facilitative role, and in fact this was raised by a number of interviewees as a particularly challenging aspect of the trial. This is primarily because pharmacy departments generally work with drugs, and are unfamiliar with the different requirements of cell therapies, as Interviewee 12 explained:

> "How do you deal with these things coming into pharmacy that they're just not familiar with? What is the minimum the pharmacist needs to know, how do you inform the use of medicines committee about something that they've never even thought about before?" (INT12)

This experience was not universal however; just as some trials used existing NHS facilities to process the cells, it appears that in some cases existing pharmacy facilities are also sufficient, as in the situation Interviewee 15 describes:

> "Between pharmacy and blood transfusion and systems in a hospital they're dealing with that sort of thing all the time … it probably depends on the hospital, so this is a very big biomedical campus, with a thousand trials going on." (INT15)

These findings suggest that, as with cell processing, the suitability of existing pharmacy facilities will vary depending on the novelty and complexity of the therapy.

Interviewee 12 gave a very clear description of the way that a complex cell therapy can be challenging for a pharmacy department to manage during a trial:

> "I'm going to ship something on nitrogen with an 11-day shelf life, and by the way it's going to have to stay in the nitrogen until the patient's ready to have it because they might throw a temperature, so you don't know when you're actually going to give it to a patient. Oh, and by the way when it comes out someone's got to thaw it, someone's got to draw it up someone's got to …" (INT12)

He went on to describe how in order to overcome these issues he visited each trial site individually to talk to the pharmacist and discuss how the process would work, which appeared to have been received positively:

> "They were really excited because it was completely different, but they were also really relieved that they weren't having to solve the problem." (INT12)

It appears, then, that hospital pharmacy departments are generally capable of handling simple cell therapies, but can struggle with more complex and unfamiliar products, and again communication is key to overcoming this.

The problem of pharmacists being unfamiliar with cell therapies was also experienced by interviewees who manufactured their cell therapies on site. Most academic and clinical setting have no experience of arranging IMPs to be signed off by a QP, and this is exacerbated by the scarcity of QPs who are trained to sign off cell therapy products, as they have generally only needed a pharmaceutical background. Trialists have found different ways to overcome these problems, but these solutions often create additional complications. It took the ENABLE team over a year to secure

the services of a QP who specialised in cell therapies, but once they did he was clearly a very valuable resource as he had a great deal of experience of ATMP regulations and trial requirements. However, they still experienced difficulties because the QP was not local and worked with a number of other labs around the country, so he was only able to visit the site occasionally. This created timing constraints for signing off cell batches, limiting the capacity of the lab and therefore the number of patients they could treat, and towards the end of my fieldwork they were starting to discuss the possibility of recruiting their own QP.

Bringing pharmacy expertise in-house was the approach taken by Interviewee 9, who had problems finding a local QP and so arranged for one of the hospital pharmacists to be trained to sign off cell therapies. This overcame the issue of availability, but he worried that it placed an unfair burden on the pharmacist because she had no previous knowledge of cell biology:

> "We had to train our own in the end … and on the whole she's been very helpful. But you know she's not an immunologist, she's never worked with cells before, and yet she's the person who has to sign off all our products." (INT9)

As these experiences show, the scarcity of specialised QPs for cell therapies is another example of the absence of a coordinated infrastructure for cell therapy trials. This means that each trial has to develop its own workarounds, which can themselves cause additional complications.

The final domain I observed as an important factor in the ENABLE trial is the world of evidence-based medicine (EBM) itself. The EBM domain is expansive and diverse, involving (amongst other things) journals, clinical guidelines, clinical researchers, statisticians, ethics and regulatory standards, methods experts, CROs, trials units and clinical research experts. Clearly, all clinical trials interact with the EBM domain in many different ways, and at different times in the process. Many of these interactions concern the way evidence is generated, interpreted and used, which I will discuss in detail in Chapter 7. From a day-to-day practice point of view, however, the most important interaction appears to be with trial methodologists,

generally either in-house statisticians or trials units, and it is this relationship that I shall focus on here.

Unlike large pharmaceutical companies, investigator-led trials tend not to have in-house trial methods specialists, and in fact ENABLE was the only example I saw of a cell therapy trial team including such an individual. However, a number of interviewees mentioned getting support from the hospital or university trials unit; for instance, Interviewee 9 said:

> "They were co-applicants on the grant as well. I mean it was a Phase 1, it was reasonably straightforward to be fair - it was just a simple dose escalation study. But they did help us, and they helped us a bit with the statistics." (INT9)

Another interviewee described using an existing research unit, which provided not only methodological support but also the infrastructure to run the trial:

> "We have a medical oncologist here … who leads the Phase 1 unit - so for early phase cancer trials, small molecules antibodies etc. So the trial is going to run within his infrastructure as it were ... that will be the structure that will help." (INT5)

It appears, then, that despite not having experience of setting up and running trials, investigators are often able to access resources within their institutions to support them in the process. It should be noted, however, that the substantial institutional support available for cancer trials that Interviewee 5 describes was unusual; other clinical areas were more likely, like Interviewee 9, to have received more limited support in trial design and statistical analysis.

Although the support available from trials units and statisticians appeared to have been welcomed by most of the investigators I interviewed, they also reported some challenges they experienced when interacting with such an unfamiliar domain. As I saw in my ENABLE fieldwork, there appears to be a communication barrier between the two areas, as exemplified by this quote from Interviewee 7 (a clinical scientist):

> "Statisticians have a particular way of talking, and you think 'I have not the faintest idea what you're talking about.'" (INT7)

This lack of understanding is apparent amongst trial specialists as well, as exemplified in this quote from Interviewee 8 (a trial manager):

> "Trying to get to the point of a statistical analysis plan with the basic scientists is a challenge, shall we say. Sometimes I think are we speaking French and they're speaking German, because we really are such poles apart." (INT8)

The analogy of speaking different languages is particularly notable here, given that this is also often used to describe the relationship between clinicians and scientists in translational research, and is also of course reflected in the concept itself.

The language barrier between EBM and clinical or scientific cell therapy researchers is most likely due to a lack of experience on both sides of what the other is trying to achieve. On the one hand, clinicians and scientists generally have at best a hazy understanding of the EBM framework, and most trials specialist have no experience of cell therapies or regenerative medicine. This means that there are very few trial specialists who really understand the needs of a cell therapy trial; for instance, Interviewee 8 confirmed that her trials unit had never managed a cell therapy trial before, and Interviewee 14 reflected that:

> "I'm going around a lot of cancer specialist centres at the moment, and there are cancer clinical trials units that are highly specialist in that. And thinking about it, how many cell therapy clinical trials units are there in the UK? You know, I don't know of any." (INT14)

It appears, then, that the ENABLE trial was extremely unusual in having a statistician working as an embedded member of the team, and who could understand the needs of the trial from both an EBM and a cell therapy perspective. It is also notable that in this quote we again see evidence of the extensive support available for cancer trials, and how this contrasts with the non-existent infrastructure for cell therapies.

5.4.2 Summary

This analysis of the interview data suggests that the relationship between the five key domains I identified in my ENABLE fieldwork is an important factor in most cell therapy trials. These findings suggest that there are two key issues that emerge from the involvement of these different areas: firstly, that cell therapy trials require domains to work together in ways that they have not needed to previously; and secondly, that these domains often don't have experience of cell therapies, and/or don't have experience of interacting with the other domains. This can cause difficulties at an institutional level; for instance, academic institutions may be reluctant to fund the kind of QA work needed to make GMP work, and basic scientific research funders may be unwilling to accommodate the unfamiliar requirements of clinical research. It can also cause problems at a team level: with individuals struggling to understand the 'language' of the other domains, it can be difficult to align goals and work towards a common cause. This is a familiar theme from sociological accounts of translational research; for instance, Wainwright et al. (2006) discuss the significant institutional and cultural differences between the scientific and clinical domains, and Brosnan and Michael (2014) highlight the importance of 'porosity' between these two domains for the successful translation of cell therapies. These accounts generally focus on the importance and challenges of the relationship between the laboratory and the clinic; my research supports these findings, but also suggests that when it comes to cell therapy translation, more consideration needs to be given to the role of other domains - cell manufacturing, EBM, and pharmacy – in trials. Pharmacy appears to play a primarily facilitative role, but cell manufacturing and EBM also appear to have a role to play in the innovation process itself, and with this in mind I will revisit these areas in more detail in Chapters 6 and 7.

The involvement of these disparate domains, and their unfamiliarity with each other and/or with the treatment area, introduces a level of complexity that is not usually found in drug trials. Multi-disciplinary working itself, however, is not uncommon in healthcare (Leathard, 2003), and although it is promoted as being a more holistic and effective way to treat patients, many authors have described the challenges experienced when members of different disciplines, or professions, need

to work together (see for instance Pietroni, 2009; Fournier, 2000; Wainwright et al., 2006). In order to smooth the interactions between different disciplines, regular communication is seen to be crucial, and this was certainly apparent in my research, where the regular meetings of the ENABLE team contributed significantly to the success of the trial. In contrast, interviewees involved in trials that did not have this type of close and regular interaction reported numerous problems working with and understanding other domains. This finding aligns with the work of Edwards et al. (2011), who coined the term 'science friction' to describe "the difficulties encountered when two scientific disciplines working on related problems try to interoperate." They go on to explain the challenges experienced due to this friction: "Every movement of data across an interface comes at some cost in time, energy, and human attention. Every interface between groups and organisations, as well as between machines, represents a point of resistance where data can be garbled, misinterpreted, or lost." Their work, which also highlighted the importance of regular meetings in overcoming this 'friction', confirms two key conclusions that I have drawn from my own research: firstly, that the interdisciplinary nature of cell therapy trials means communication problems are to be expected; and secondly, that close interaction between the domains involved can help to overcome this to some extent.

From a normative perspective, then, it would be beneficial for more cell therapy trials to follow the model I saw in the ENABLE trial, where members of the different domains involved in the trial met on a regular basis, and where trials specialists (including the statistician and trial manager) were integral members of the team, and so familiar with the specific needs of a cell therapy trial. This model is reminiscent of the situation Keating and Cambrosio describe during the development of the modern trials framework during the 1960s, when rather than remaining at arm's length, statisticians became part of the clinical area they studied. Importantly, the embedding of statisticians affected the way that the research was conducted: "Statisticians working within the cooperative groups were not simply technicians hired to crunch numbers. Knowledge of the field in which they worked did make a difference in how they evaluated and analysed the data" (Keating and Cambrosio, 2012, p.150). The value of this for cell therapy trials is clear, as there is a need for

trial design to accommodate both the specifics of the clinical area and the specifics of a cell therapy treatment. A statistician who understands both of these issues, as John did for the ENABLE trial, will be able to understand the needs of the cell therapy developers and 'translate' these into the trial design, whilst also helping the rest of the team to interpret the confusing world of EBM. It is important to recognise, however, that such a model has sociological implications: as Keating and Cambrosio's work shows, the involvement of statisticians was part of the development of a specific style of practice in clinical oncology, and this is the model that has underpinned the problematic framework of evidence-based medicine which I will discuss in Chapter 7. For now, however, it is sufficient to note that greater engagement with trials specialists is likely to facilitate individual cell therapy trials, but it will also further embed the field within a particular evidentiary framework which may not always be appropriate or constructive.

5.5 Discussion

I noted in the introduction to this chapter that the existing literature, whilst not comprehensive, suggests that funding constraints and the length of time required are two aspects of the 'doing' of trials that are problematic for cell therapy translation. My findings support this conclusion, and also suggest that working with cells, which is recognised as another translational challenge, has implications that create specific challenges in a trial context. My findings also suggest another specifically challenging aspect of trials which has to date received less recognition: the need for numerous disparate domains to work together. What is particularly notable from my findings, however, is that whilst each of these issues might be challenging in their own right, they also interact with each other to create further complications. Thus, the financial aspects of the trial can be challenging because the available funding is often not sufficient for running a highly-regulated drug trial, and also because the expectations of funders may not be aligned with the realities of cell therapy trials. Reimbursement is problematic because the way excess treatment costs are funded on public trials means that trialists often need to make an economic case for a treatment that has not yet been proven to work, and added to this is the

fact that the time required to undertake the trial might be much longer than expected, further exacerbating funding issues. Temporality also creates problems in terms of path dependency, as developments in scientific knowledge might outpace the treatments that are being tested in the clinic, which is linked to the unpredictable nature of working with living cells as a therapeutic agent. This also introduces uncertainties into the manufacturing process, creating additional funding constraints, and also introducing a new domain into the trial – manufacturing – which would not normally be so closely involved in a clinical trial. And there are also other domains involved, such as pharmacy and trial methods, that are not used to dealing with cells, creating barriers in terms of the trial itself as well as the long-term development of the treatment.

It seems, then, that cell therapy trials face a specific set of challenges, and also that these challenges interact with each other to create further complications. This is not to say, however, that these challenges will be consistent for all cell therapy trials; in fact, my findings suggest that the opposite is the case, because whilst the challenges and interactions I have discussed were all apparent in many of the cases I studied, none of them were universal. Each trial appeared to have a distinct configuration of challenges, with some being more or less important, or experienced in a distinctive way, and with different links and interactions between them. This further emphasises the heterogeneity of the field that I have highlighted in previous chapters, and reinforces the point that there is unlikely to be a 'one size fits all' model appropriate for all cell therapy trials. Likewise, most of these challenges are not unique to cell therapy trials: for instance, excess treatment costs have been a significant issue in many publicly-funded trials, and interaction between different domains is often a factor in complex intervention trials. However, the scale of these challenges, as well as their interaction with each other, does appear to be particularly problematic in trials of innovative new treatments such as cell therapies. For instance, whilst excess treatment costs are a general problem, they are particularly challenging in cell therapy trials where the costs are often high and the treatment is likely to be unproven. And whilst complex intervention trials may involve interaction between a number of different domains, these tend not to be CTIMPs and are

therefore not subject to such strict regulations, and are also unlikely to involve fast-paced scientific research taking place alongside much slower clinical trials. We can conclude, therefore, that cell therapies do tend to face a distinctive combination of challenges that make trialling more problematic than in other fields, although the specific combination of factors will differ depending on the characteristics of the therapy and trial setting.

Having identified the main challenges faced by cell therapy trials, we can also consider the implications of these challenges, perhaps the most pertinent of which is the variety of actions, negotiations and deviations that trialists undertake throughout the trial in order to make it work. Cell therapy trials are clearly not fixed entities, but continually evolving practices that shift to accommodate clinical realities, scientific advances, changes in regulations, unexpected obstacles and a host of other unforeseen eventualities. Furthermore, trialists are attempting to build flexibility into the trial protocols themselves, both to accommodate the complexity of working with uncertain cells and to address the issue of path dependency. These contingencies reflect an additional dimension that enters the research vs. care dynamic when the treatment being tested is a cell therapy: the clinical needs of the patient must be balanced not only against the research needs of the trial, but also against the scientific complexity and technological challenges introduced by using a complex living organism as a therapeutic agent. Clearly, then, the apparent rigidity of a trial protocol masks a messy and complex process that is far from the 'controlled' experiment of EBM rhetoric, and the supposedly neutral and objective final outcome measure does not even begin to tell the full story of the trial. Although at odds with the prevalent EBM orthodoxy, this is not surprising in the context of the sociological literature, which has frequently highlighted the provisionality of trials (see for instance Will and Moreira, 2010; Sismondo, 2008; and Daly, 2005). This provisionality is if anything amplified by the specific challenges of working with cells, with particular implications for innovation in the field, as we shall see when we look more closely at the concept of evidence in Chapter 7.

As well as increasing the provisionality of the trial, the challenges faced by cell therapy trials are make it easier to trial some cell therapies than others. For instance,

the money and experience needed to set up GMP facilities means that it is far easier to set up a trial using existing infrastructure, which favours cell therapies that are similar to existing treatments, and those that fit in best with existing processes. Likewise, the fact that funding is so difficult to source means that those treatments that can make (or promise) an economic case are more likely to get trialled than others. It appears, then, that the cell therapy trials framework favours incremental change through building on existing knowledge, particularly as many of the domains having to interact together are unfamiliar with the terrain. This aligns with sociological accounts of innovation as an incremental and recursive process rather than a diffusion of technological advancement (a topic I will discuss in some depth in the next chapter). However, another important factor is the length of time it takes to do these trials, which creates a time-lag between science and clinic that makes it difficult to respond quickly to new developments. Trialists are therefore attempting to anticipate these changes and future proof their work, and in some cases trials will continue even when the scientific basis for the treatment has been disproven. Thus, whilst trials may favour incremental innovation, they also impose a linear model that does not facilitate recursive learning and feedback. This causes particular problems for the translation of cell therapies, as we shall see in the next chapter.

6. Managing uncertainty: "we're in wild west territory"

As well as the excitement stimulated by breakthroughs in the basic science of stem cells, the past two decades have also seen growing concerns about the widespread availability of unlicensed treatments. In the UK, unlicensed ATMPs can be produced under Hospital Exemption (HE), and those that are not designated as ATMPs are generally only subject to the less stringent regulations for medical devices, blood transfusion or organ transplantation. Other countries have varying levels of regulation and oversight, with some having almost no restrictions, prompting so called 'stem-cell tourism', whereby patients travel abroad for treatments that they cannot access in their own country (Petersen et al., 2017). This has caused consternation amongst the clinical and scientific communities, as reflected in this quote from Interviewee 12:

> "There are more tissue engineered products and stem cell products available - untested, but commercially available - around the world than there are licensed ones, than there are regulated clinical trials. And that's not true of any other product, you know - we're in wild west territory." (INT12)

As this quote highlights, concerns about unregulated cell therapies have tended to focus on commercial providers; for instance, Daley (2012) cautions that sponsored websites "peddling cures for ailments as diverse as Alzheimer's disease and autism … systematically overpromise the potential efficacy of stem cells and trivialize the potential risks." The recent controversy surrounding the Stamina Foundation in Italy highlighted the discord between the scientific community and unregulated commercial clinics (Bianco et al., 2013a), and demonstrated how difficult it can be to restrict access to commercial treatments when patients themselves are demanding access to them. The public sphere has not been immune to these concerns, as highlighted by the recent case of Paolo Macchiarini. One of the highest-profile surgeons involved in regenerative medicine, and a pioneer of synthetic tracheas seeded with bone marrow-derived cells, Macchiarini was found to have misrepresented pre-clinical and clinical results, and continued to treat patients

despite mounting evidence that the treatment was ineffective and potentially dangerous (Nature, 2016). His employer, the prestigious Karolinska Institute in Sweden, was accused of failing to subject his work to adequate oversight, and of failing to address concerns about him when they were raised. The case has significantly affected confidence not only in the tissue-engineered tracheas he was associated with, but in the field of regenerative medicine as a whole.

These concerns about the use of unlicensed therapies can be understood as part of a wider tension surrounding the translational medicine agenda in cell therapies. Translational medicine, or the process of using basic scientific research to develop effective medical treatments, is seen as crucial for medical progress (Marincola, 2003), forms the focus of much technology and scientific policy (Martin et al., 2008), and strongly shapes the research agendas of both the UK Medical Research Council and the US National Institutes of Health (Wainwright et al., 2006). The translational agenda is nowhere more evident than in stem cell research, where policymakers have emphasised its role in improving the competitiveness of national capabilities in regenerative medicine - see for instance the House of Lords report (2013), which urged the government to improve the UK's capacity for clinical research in the field. There is also a proliferation of initiatives aimed at facilitating translational stem cell research, for instance the Cell and Gene Therapy Catapult, the UK Stem Cell Bank, and the Arthritis Research UK Tissue Engineering Centre. The seminal importance accorded to translation is perfectly articulated by Mason (2007), who describes what he sees as a new paradigm appearing in the regenerative medicine field: "the pioneers were all about the science and research and little about translation into genuine products with benefits to both patients and shareholders. Whereas RegenMed 2.0 is almost exclusively focussed on the pragmatic translation of great science into routine clinical practice." Proponents of the translational agenda prioritise clinical research over basic science because of both the need to prove clinical and commercial success in order to attract funding, and a view that good clinical research will facilitate basic scientific understanding (Mason and Dunnill, 2007). Notably, as Prainsack et al. (2008) point out, the rhetoric

underpinning this perspective relies on the assumption that therapeutic success in regenerative medicine is 'out there' to be found; like the first scaling of Everest, the peak was always there and the challenge was simply getting to it.

The hype around cell therapies tends to skim over the complexities and uncertainties of basic scientific research, because, in the words of a former science editor for the Guardian, "you don't grab headlines by describing embryo stem cell research as an expensive laboratory-based technology guaranteed to lead to many years of frustration and small flashes of enlightenment" (Kitzinger, 2008). The scientific literature, on the other hand, paints a cautious picture, leaving the reader with a sense that the search for revolutionary cell therapies is less like climbing Everest and more like the early settling of the Pacific Islands: setting off into uncharted ocean looking for land, without knowing how far away it might be or in which direction, or indeed whether it even exists. In light of this uncertainty, many scientists prioritise basic research over early clinical testing; for instance, Daley (2012) argues that scare research funds should be spent on bench research, because without better scientific understanding clinical research will largely just be trial and error. Similarly, Braude et al. (2005) criticise clinical trials of poorly-understood cell therapies, arguing that "urgency is not an excuse for bad science." Experimenting in the clinic is viewed negatively by many scientific researchers because of the high likelihood of failure, as highlighted by this scientist quoted in Cribb et al. (2008): "They basically said, 'Oh we've got some sick patients, got some cells, chuck one into the other and see what happens.' With absolutely no biology behind it at all! And, of course, it didn't work. It's not surprising." Such a high failure rate is seen as difficult to justify ethically, and risks eventual disillusionment in the field; for many, therefore, it calls into question the wisdom of the entire translational agenda.

It seems, then, that the dynamics of cell therapy translation are shaped by two competing perspectives: one which emphasises potential and pushes for progress, and the other which highlights uncertainty and urges caution. The second, cautious approach, is particularly concerned with the unregulated use of cell therapies, in particular for commercial gain, but also argues against the

premature use of cell therapies even within regulated clinical trials. Traditionally, a trial is used to test the safety and efficacy of a new treatment, and even in a Phase 1 trial there is generally little uncertainty about the basic underlying science. For cell therapies, however, trials take place in circumstances of significant *scientific uncertainty* (i.e. lack of knowledge or consensus about the basic science), as well as associated *clinical uncertainties* (i.e. uncertainties about how the therapy will work when it is given to a patient). In the first section of this chapter I will explore these two types of uncertainty, and I will then discuss in the second section the various ways that trialists attempt to resolve or reconcile them. In the concluding section I consider how these uncertainties in cell therapy trials, and the ways that trialists attempt to resolve them, relate to the overall process of translation and innovation.

6.2 Uncertainty from bench to bedside

One of the defining features of stem cell research over the past two decades has been the rapid changes in scientific knowledge. Scientists now know significantly more about the biology of stem cells than they did 20 years ago, and can do much more to manipulate them, but with this increased knowledge come further uncertainties and complexities. For instance, it is just over ten years since Yamanaka first described the process of reprogramming somatic cells into a pluripotent state, and since then significant progress has been made in understanding and refining the process (Yamanaka, 2012; Kimbrel and Lanza, 2016). However, as Yamanaka highlights, these developments have raised many further questions that are now being explored, and fundamental uncertainties remain, such as the extent to which induced pluripotent cells differ from embryonic stem cells, and whether any such differences have a functional effect. Biological stem cell research, then, is characterised by both rapid progress and by significant and ongoing uncertainty. This uncertainty can be both known (i.e. scientists are aware of the issue but have not yet resolved it, as is the case for the queries Yamanaka raises), or unknown (i.e. some future development will change current understanding in a way that is not yet understood or anticipated).

Uncertainty is, of course, an inherent and accepted part of basic scientific research - as Carl Sagan and Ann Druyan (1992, p.xiv) eloquently put it: “Science is

never finished. It proceeds by successive approximations, edging closer and closer to a complete and accurate understanding of nature, but it is never fully there." Scientific uncertainty is problematic for translational research, however, because it can hinder attempts to develop an effective treatment and understand how it works, as highlighted by Interviewee 12's description of the development of T-cell therapies during the 1980s:

> "And in those days, we thought that there were two types of T cells – there were T8 cells and there were T4 cells. And in 1984 … we saw our first patients who had literally no circulating T4 cells, and we couldn't understand why … This was the beginning of the AIDS problems, and these were the early AIDS patients … and someone had the smart idea that we could isolate T4 cells and give them doses of their own T4 cells back. Now we believed we were giving them pure T4 cells, and we were - but one product might have had 90% central memory cells and 10% terminal effective cells … now we know there are 170/180 different types of T4 cells." (INT12)

Added to, and to some extent stemming from, uncertainties in the basic science are a variety of what could be termed clinical uncertainties, which materialise when cells are used in the clinic. Clinical uncertainties can relate to the manufacturing of cell therapies, and the way that cells behave when administered *in vivo*, and also to uncertainties regarding individual patient response, disease epidemiology and variable institutional settings. Later in this section I will look at the various ways that trialists experience clinical uncertainty, and explore how this affects the translation of cell therapies. First, however, I will examine the issue of scientific uncertainty in more detail by looking at one particular example, MSCs, which are both extensively used in the clinic and the subject of much scientific uncertainty, and even controversy. Drawing on secondary data, including scientific publications and public engagement material about MSCs, I will examine the various different perspectives on the basic science, before then drawing on data from my own research to demonstrate how these different perspectives are enacted in the context of clinical research.

6.2.1 Scientific uncertainty: "Most Suspicious Cells"

MSCs are typically described as multipotent cells that can self-renew and differentiate into bone, cartilage or fat, and in the scientific literature this description might be extended to include other features, such as plastic adherence, morphology and antigen expression. Figure 6.1 gives examples of typical descriptions of MSCs from both scientific papers and public engagement material, and Figure 6.2 details the official criteria adopted by the International Society for Cellular Therapy.

Figure 6.1: Descriptions of MSCs

> "Mesenchymal stem cells (MSCs) are an example of tissue or 'adult' stem cells. They are 'multipotent', meaning they can produce more than one type of specialised cell in the body, but not all types. MSCs make the different specialised cells found in skeletal tissue. For example, they can differentiate - or specialise - into cartilage cells (chondrocytes), bone cells (osteoblasts) and fat cells (adipocytes)." (Eurostemcell, 2017)
>
> "MSCs are self-renewal cells with the potential to differentiate into cells of the adipogenic, osteogenic, and chondrogenic lineages." (Ezquer et al., 2015)
>
> "Mesenchymal stem cells (MSCs) are defined by their fibroblast-like morphology, adherence to plastic, expression of a specific set of surface antigens (CD105+, CD90+, CD73+), and capacity for osteogenic,

Figure 6.2: ISCT criteria for identifying MSCs (Dominici et al., 2012)

1	Adherence to plastic in standard culture conditions		
2	Phenotype:	Positive (≥95% +) CD105 CD73 CD90	Negative (≤2% +) CD45 CD34 CD14 or CD11b CD79α or CD19 HLA-DR
3	*In vitro* differentiation: osteoblasts, adipocytes, chondroblasts (demonstrated by staining of *in vitro* cell culture)		

Although initially isolated from bone marrow, other sources of MSCs are now widely recognised. Keating (2012) reports that MSC populations can be "obtained readily" from a variety of tissues, including placenta, skin, umbilical cord, dental pulp, synovial membrane and breast milk. Ren et al. (2012) state that "MSCs from other sources, such as umbilical cord and adipose tissue, are also able to be expanded in vitro rapidly with sustained stable phenotype and differentiation potential toward several mesenchymal lineages, such as fat, cartilage, and bone."

Several papers have reported the number of MSC therapies currently being trialled in the clinic (see for instance Li et al., 2014; Wei, 2013 and Daley, 2012), and although the exact number varies between sources, they all report that MSCs make up a large and growing proportion of current cell therapy trials. For instance, Li et al report that MSCs represent 41% of global stem cell trials, and account for the majority of the increase in novel cell therapy trials between 2006 and 2011. Most current MSC trials use bone marrow-derived cells, but the use of cells sourced from other tissues is increasing; for instance, Ezquer et al. (2015) report adipose and cord-blood derived cells being trialled for cardiac regeneration, and the ADIPOA trial used adipose-derived cells as a treatment for osteoarthritis. MSCs are being trialled for a wide range of clinical indications, including musculoskeletal conditions, cardiac repair, stroke, auto-immune diseases and multiple sclerosis. MSCs were also the first stem cell treatment worldwide to receive a marketing authorisation, with the Canadian regulator approving Prochymal in 2012 for the treatment of graft versus host disease in children (Wei et al., 2013).

The relatively straightforward descriptions of MSCs given in many scientific papers, along with their widespread use in the clinic, can give the impression that these cells are well-understood and uncontroversial. In fact, however, the opposite is the case: there is substantial debate amongst the scientific community about the biological properties of MSCs, to the extent that there is no consensus even about what they are. The acronym MSC is most often taken to mean mesenchymal *stem* cell, but the ISCT definition refers instead to mesenchymal *stromal* cells, on the basis that not all of the population defined will be stem cells (Keating, 2012). There are also arguments for the 'M' in MSCs referring to *multipotent* rather than

mesenchymal, and in some cases the two different descriptions are even used within the same paper, for instance Nuschke et al. (2014) refer to "bone marrow mesenchymal stem/multipotent stromal cells (MSCs)". The term 'skeletal stem cell' has also been proposed as a more appropriate description for non-hematopoietic stem cells in the bone marrow (Eurostemcell, 2017; Bianco et al., 2013b). It is not clear, however, whether this term could also be applied to MSCs derived from other tissue, and indeed there is also debate over whether such cells can properly be categorised as MSCs at all (Bianco et al., 2013b; Keating, 2012).

These disagreements about what the cells should be called reflect a deeper uncertainty about what they actually are. Bianco et al. (2013a) argue that "the artificial properties seen as 'defining' features of MSCs [i.e. the characteristics set out by the ISCT] are simply widely shared properties of connective tissue cells. They do not imply any true stem-cell property or the true ability to form bone, cartilage or adipose tissue *in vivo*." Keating (2012) shares this concern about artificiality, arguing that "MSCs as currently defined are a phenomenon of *in vitro* culture, suggesting that extrapolating the function of these cells to activity *in vivo* must be done with caution." More recently, the well-publicised immune-modulatory properties of MSCs have prompted further queries over their classification, for instance Hoogdijin (2015) argues that they could in fact be described as immune cells, as their immunomodulatory properties "raise the academic question whether MSCs are immune cells or whether they are tissue precursor cells with immunoregulatory capacity." Inevitably, these uncertainties about the definition and characteristics of MSCs have resulted in widespread inconsistencies in the way that the basic scientific research is conducted and reported. Bianco et al. (2013a, p.1493) warn that "loose definitions and poor assays have disseminated across the scientific community as 'gold standards'", and Keating (2012, p.709) argues that "confusion arising from the definition of the MSC population made comparisons among published studies in the 1990s and 2000s problematic." Keating goes on to explain that the absence of a specific marker to define MSCs has been a particular challenge for the field, and although Bianco et al. claim that the mesenchymal, or skeletal, stem cell is a "precisely defined physical and conceptual entity", this precise definition excludes a

significant proportion of current research on MSCs, and thus appears to be at odds with current mainstream scientific opinion.

Regardless of the scientific validity, or otherwise, of these different perspectives, these disagreements and inconsistencies can make it difficult to evaluate and compare scientific research on MSCs, because the term itself can mean different things, and it is often not possible to ascertain from a published article exactly which definition the authors have used. Uncertainty in the reporting of the basic science also filters through to clinical MSC research, with Liao and Tse (2013) reporting a "high degree of heterogeneity in terms of cell population, dose, preparation and delivery methods" in clinical trials. Studies examining clinical trial activity have also approached MSC trials in different ways: for instance, Foley and Whitaker (2012) exclude them from their analysis because "mesenchymal stem cell therapies are based on immunomodulation and not cell replacement", a view which, as I will discuss, below is not universally held. In contrast, Li et al. (2014) include MSC trials in their study, but do not fully explain exactly what types of therapies they categorise as being MSC-based, explaining only that "most MSC trials explicitly labelled their SC type as mesenchymal, but some did not." They do explain that they categorised cells described as 'adipose-derived stem cells' as MSCs, whilst recognising that "in some of these CTs, the transplant may be of lipoaspirates, with the therapeutic effect due to the presence of MSCs", and they also warn that "adipose-derived MSCs likely have different properties from those derived from bone marrow." A further complication relates to the treatment of bone marrow-derived mononuclear cells, which will include a variety of cell types including MSCs and hematopoietic stem cells (HSCs). Li et al include 'mononuclear fraction' within their HSC category, and thus a trial such as BAMI - which describes the cells used as "autologous bone marrow derived mononuclear cells" - would be categorised as an HSC treatment. The therapeutic effect of such treatments, however, is generally presented as being due to the MSCs present in the fraction, although as I shall discuss later this in itself is a subject of much debate and disagreement. It is only through Li et al.'s admirably clear and thorough reporting of their methods that these complexities become apparent, but they clearly affect any study that aims to collate

and compare clinical trials using MSCs, including not only research examining the number and characteristics of such trials, but also systematic reviews of their results.

Linked to these uncertainties about the definition and characteristics of MSCs is a contested, and changeable, understanding of their potential clinical applications. Broadly speaking there are three therapeutic possibilities that have been explored for MSCs: 1) differentiation into bone or cartilage, 2) differentiation into other cells, and 3) paracrine, anti-inflammatory or immunomodulatory actions (Daley, 2012). Daley argues that only the first of these is founded on strong preclinical evidence and sound scientific and clinical hypotheses, although even here he points out that "evidence for robust clinical efficacy of MSCs for orthopaedic indications has been challenging to confirm." The potential for MSCs to regenerate anything other than musculoskeletal tissue has largely been discredited over the past ten years, with most scientists now of the opinion that MSCs do not differentiate outside of the mesenchymal lineage *in vivo* (Genever and Fox, 2014). Observed regenerative effects of MSCs are now thought to be more likely due to the third of Daley's mechanisms, i.e. their paracrine, anti-inflammatory or immunomodulatory actions, but in this area also there is still uncertainty and controversy. Daley argues that although there is evidence of efficacy in the literature this is also mixed with negative results, and he warns that the precise role of MSCs in immune-modulation remains to be proven. Bianco et al. (2013b) go further than this and argue that even if such effects do exist, they cannot justifiably be described as either stem cell-based or regenerative, as the cells "are neither transplanted nor engrafted and do not regenerate tissues." Uncertainty over the mechanism of action is viewed by some as problematic for translation; for instance, Keating (2012, p.713) notes that a number of trials are still in progress that are testing MSCs based on cell replacement rather than a paracrine or anti-inflammatory mechanism. He argues that "the study outcomes are unlikely to be optimal if the major effect is actually an anti-inflammatory one and may arise from a number of factors including inappropriate dose, scheduling, or route of administration. Furthermore, the co-administration of anti-inflammatory agents may be a confounding factor." Keating also argues that progress in understanding the mechanisms of MSC-based treatments "may have been limited to some extent by

the concept of the mesenchymal ‘‘stem’’ cell and the implicit idea that the objective was cell ‘‘replacement’’ therapy.”

Unsurprisingly, these uncertainties in the scientific literature mean that there are conflicting narratives about how promising MSCs are in the clinic. Some authors make sweeping claims for clinical efficacy, for instance one review paper states: “In preclinical and clinical studies, MSCs *have been shown* to be *highly efficient* in treating graft versus host disease, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, myocardial infarction, liver cirrhosis, inflammatory bowel disease, and other disorders” (Ren et al., 2012). Interestingly, this quote is taken from the paper’s abstract, and does not entirely reflect the much more nuanced account of the clinical studies presented in the full text. Nevertheless, given that the abstract sets the tone for the rest of the paper, and often may be the only part that is read, the language used is likely to suggest to the reader that the efficacy of MSCs is both significant and proven. Others are much more cautious in their view of efficacy, however, as shown in this excerpt from Bianco et al. (2013b): “A number of therapies have been *envisioned* for the treatment of diverse disorders and diseases, such as diseases of the CNS, GvHD, cardiovascular diseases, pulmonary diseases and many more … It is thought, but as yet *unproven*, that they may exert paracrine, immunomodulatory and immune-regulatory effects on endogenous tissues upon systemic infusion or direct injection.” There are also conflicting views about the safety of MSCs; it is sometimes suggested that, unlike embryonic stem cells, they are free from the risk of immune rejection and teratoma - for instance Ezquer et al. (2015) state that “they are not rejected by the recipient’s immune system, even if they come from a non-histocompatible individual”, and Wei et al. (2013) claim that they have “low immunogenicity and no teratoma risk.” These interpretations are contested by others, however, for instance Bianco et al. argue that “as inherently osteogenic and adipogenic cells, MSCs could generate bone or fat in the wrong organs if transplanted in sufficient numbers”, and that “allogeneic MSCs can trigger an adverse reaction.” Clearly, then, there are differing interpretations of the safety and efficacy evidence for MSC therapies, and, in conjunction with continuing

uncertainties in the basic science, this results in a complex, contested, and changeable environment for clinical trials.

6.2.2 Translating uncertainty: MSC trials in the UK

My fieldwork confirmed the popularity of MSC-based treatments, which, as I reported in Chapter 3, represent almost a fifth of UK cell therapy trials (rising to a quarter if we include trials using unspecified bone marrow cells). My interviews suggested a number of reasons for this popularity. For some interviewees, MSCs were seen as a proven, effective therapy - for instance Interviewee 6 said of their use for GvHD: *"It's just spectacular how well they work."* There also appears to be a general acceptance that, despite a theoretical risk of teratoma formation, in practice MSCs have been shown to be safe – a view exemplified here by Interviewee 11:

> "Long-term follow up is always the big thing. Obviously you're giving people cells, there's the potential to morph into some other kind of cells, form ectopic tissue - so you start forming bone in the heart or something like that. But no-one's ever reported anything like that with mesenchymal cells." (INT11)

The potential immune response also did not appear to be a great concern for UK trialists, even for allogeneic MSCs. Two of the eight MSC trials in my dataset used allogeneic cells, and Interviewee 6 (who produced allogeneic MSCs for use under a specials licence) emphasised the evidence that there was no concern about an immune reaction to these cells:

> "There's been safety work done, and they're very safe. They don't express HLA antigens, they're safe to be used as a third party, you know. People have gone through the concept of maybe we should have HLA typing, and they've now reached the point where we know third party donors is very safe."

In addition to this reputation for safety and efficacy, MSCs are also appealing because of the theoretical possibility that they could be used to treat a wide variety of different conditions, as highlighted by Interviewee 16:

> "MSCs is the flavour of the moment, and we give MSCs for anything I can think of under the sun - let's repair the skin, let's treat graft versus host disease, maybe we can treat diabetes with this, maybe we can treat the back of the eye for blindness and all of that." (INT16)

Practicality may also play a part in the popularity of MSCs; they appear to be seen as a relatively simple cell therapy that is easy to manufacture – for instance Interviewee 10 described them as *"a relatively straightforward product"*. It seems, then, that there are both clinical and logistical reasons for the prevalence of MSC trials.

The ease of producing MSCs, along with their perceived applicability to a wide range of conditions, appears to have encouraged an approach to innovation that could be loosely be described as 'technology push', as described by Interviewee 16:

> "I think in terms of the commercial ventures at the moment, people are taking cells that can be produced and then trying them in different conditions, rather than producing the cells specifically for a particular condition." (INT16)

This approach is seen as aligning with the wider policy agendas surrounding translation and innovation, as discussed by Interviewee 14, who had been involved in a knowledge transfer programme with an innovation accelerator agency. She described the way that academic researchers are under pressure to find applied uses for their research, and explained that innovators were being encouraged to develop technologies that have broad rather than niche applications:

> "You want to make sure that you're making platforms, as they call them - so you're making tools that actually extend right across companies, that are fairly ubiquitous in their use."

Although here she was specifically discussing engineering and manufacturing technologies, it is clear that this approach also relates to MSCs, which are seen as easy to manufacture, relatively low risk, and have a wide range of potential uses. This environment appears to facilitate a rather 'trial and error' approach to trialling - what

Daley (2012) refers to as purely 'empirical' clinical testing - which might be less likely if the cells were more difficult to produce, or seen as riskier to use.

Despite the general perception of MSCs being safe and potentially effective, most of my interviewees also acknowledged the uncertainty in the basic science. For instance, Interviewee 12 described the lack of consensus about their definition:

> "Now we had a three-day meeting in Washington ... to try and define what a mesenchymal stromal cell was. And after three days - it sounds very funny but it's actually true, very depressingly - the only thing that came out at the end of three days was an agreement that the C stood for a cell." (INT12)

This uncertainty was also evident in my dataset of UK trials: of the eight trials I categorised as using MSCs, three described the cells as 'mesenchymal stem cells', two referred to 'mesenchymal stromal cells', one referred to 'bone marrow-derived stromal cells', one simply used the term 'MSCs', and one described the cells as 'multipotent adult progenitor cells'. There was also a general lack of clarity about the specifics of the cell population and release criteria used, and in fact for most trials it was difficult to find any information about the cell manufacturing process at all. Commercial MSC products are often referred to in publicly-available materials by a brand name (such as 'MultiStem' or 'Cell bandage'), with little information given about the exact characteristics of the cells, and my interviewees were also careful not to disclose too much information about how they manufacture the cells. The lack of information about cell processing for industry trials is perhaps unsurprising, given the commercial sensitivity of the information, but I also found it difficult to find information about the cells used in publicly-funded MSC trials. To give a typical example, the clinicaltrials.gov entry for the ASCAT trial simply refers to 'mesenchymal stem cells' without giving any further details about the processing, selection or even source of the cells. There was significant variability between trials, however, with some providing more details than others: for instance, the entry for the STREAMS trial specifies the dose to be used, and the RegenVOX entry specifies the source of the cells and the fact that they are grown on a scaffold. None of the trials I reviewed, however, provided complete information about the cell processing in their trial

registry entries, and even in protocols or trial reports published in peer-reviewed journals this information was often missing or incomplete.

As well as a lack of clarity about the definition and characteristics of the cells being used, I also encountered a number of instances of uncertainty about the mode of action for MSC treatments. In one typical example, Interviewee 4 acknowledged the lack of solid evidence about how the treatment being tested in his trial actually worked:

> "The explanation I've given you is probably complete rubbish, you know - it's conceptual, nobody really knows how this type of stem cell transplantation really works." (INT4)

The published information I was able to access about ongoing trials generally gave very little detail about the treatment's likely mode of action, with only three of the eight MSC trials making reference to this at all. There was also evidence of the shifting scientific consensus about the differentiation potential of MSCs; for instance, Interviewee 8 provided me with a hard copy of the protocol for one of the trials in my dataset, which claimed that *"stem cells from a person's own bone marrow can develop into cells normally found in other body organs, e.g. heart muscles."* This reflects the prevailing scientific understanding at the time the protocol was written (around 2002), which was already being called into question by the time the trial started recruiting in 2008, and was certainly at odds with scientific consensus by the end of recruitment in 2012. At the other end of the scale, I also saw what might be the beginning of a further shift in the scientific consensus, when a scientist involved in an osteoarthritis trial mentioned to me that she is increasingly of the opinion that even for musculoskeletal conditions, the clinical action of MSCs may not be due to their differentiation into cartilage (Field notes 19/02/15).

Ongoing uncertainty in the basic science presents a number of challenges for cell therapy trials using MSCs, not least because lack of knowledge about the cells can hamper the development of an effective treatment. For instance, a clinician developing MSC treatments for musculoskeletal conditions explained that in order for a therapy to be scalable they need to be able to identify the MSCs that are best at differentiating into cartilage, but that scientific knowledge was not yet sufficiently

advanced for this to be possible (Field notes 01/05/2015). The heterogeneity of MSC cells populations, and uncertainty about the characteristics of different subsets within them, can also make it difficult to interpret the results of a trial, as explained by Interviewee 12:

> "In many trials we will inevitably have a situation where the outcome is less clear than with a conventional pharmaceutical, because you've not got the same degree of control in your product." (INT12)

Lack of scientific consensus is also problematic from a regulatory perspective, because without an agreed definition and specific markers for MSCs it is difficult to predict how regulators will treat a specific therapy, as Interviewee 17 explained:

> "It's more I guess from the standards perspective, you know even down to the definition of what is an MSC, because there isn't a definition of an MSC. So what cell types mean and what the regulator would let you do in terms of how far you can expand a cell population without getting into safety worries." (INT17)

It seems, then, that despite their popularity, trialists are by no means heedless of the uncertainties in the basic science of MSCs, and recognise that these uncertainties can be problematic for trials, and for the longer-term clinical development of the field.

6.2.3 Clinical uncertainty: complexity multiplied

Although the scientific uncertainties described above are particularly acute for MSCs, there are similar uncertainties in the basic science for all cells being developed for clinical use. This is then further complicated by the additional uncertainties that arise when cells are used in the clinic - what I have termed clinical uncertainties. These clinical uncertainties arise in part from the sheer complexity of 'life' in the clinic: each patient represents a specific configuration of an almost infinite number of variables, including the specifics of their diagnosis or injury, their treatment history, co-morbidities, lifestyle and demographics. This complexity is complicated by variability in patient response, which can make it hard to predict the effects of a treatment and to generalise from past experience. The importance of understanding individual

patient response is reflected in this quote from Interviewee 17, who explained that the patient's recovery from the treatment would be one of the most important things they would learn from their trial:

> "But mostly you learn about the post-operative recovery, because the one thing you can't really predict is how the patient's going to react." (INT17)

There can also be uncertainties about the condition being treated, such as how to measure severity or prognosis, as shown in this quote from Interviewee 9:

> "We haven't got very good biomarkers for what we want. In a sense, what we're trying to do is cure the patient - so you could argue well OK you treat your patients, if they get better in three weeks, or three months, or six months, and never flare again then you've been successful. But the likelihood of that happening without biomarkers to tell you that you're doing the right thing [is very low]." (INT9)

Inherent uncertainties about both patients and diseases can thus make it difficult both to predict how patients will respond and to measure this response.

Clinical uncertainties such as these are of course present in all clinical trials, but for cell therapy trials further uncertainty is introduced by the treatment itself. One of the main challenges for cell therapies is the limited applicability of animal models, which can make it difficult to predict how cells will behave when used in humans. Sometimes this can be because the disease presents differently in an animal, particularly if it is not a disease the animal would naturally suffer from. For instance, one interviewee described problems with a cell therapy that were not apparent in animal models because they were caused by an interaction with previous drug treatments that the animal would not have been exposed to:

> "Nobody had thought of ever testing a transplant in an animal to be chronically treated with [drug name] you see - when you induce [disease name] in an animal you do it with a toxin, you get acute disease, you put in a transplant and you repair it." (INT2)

For other cell therapies, animal models are not even possible: for instance, one clinician explained there is no good animal model for blood transfusion, because it is not possible to transfuse human blood into animals (Field notes 01/05/14). And even when it is possible to use an animal model, it may be the behaviour of human cells *in vivo* will not be the same in animals as in humans, as highlighted by this quote from Interviewee 12:

> "If I put human cells into an immunocompromised mouse and the mouse doesn't reject them, they're pretty much all going to deliver on the lung because that's where the circulation takes them. Put them into a human they're going to find their native adhesion molecules to stick to - they're going to behave physiologically in the human." (INT12)

Such views about the limitations of animal models were expressed by most interviewees, however Interviewee 16 had a contrasting perspective, feeling that they were relatively straightforward in his area:

> "That doesn't seem to be a problem at all. I mean, you have to choose your appropriate mouse model - we use mice that have got a very weak immune system, so they don't destroy the human cell." (INT16)

Animal models, then, appear to be problematic for many cell therapy trials, but as with so many of my findings this was not a universal experience.

A lack of appropriate animal models has significant implications for trials, because it makes it difficult to collect the pre-clinical data that is essential for gaining regulatory and ethical approval. Animal models are a fundamental step in the process, as highlighted by this quote from a clinician involved in a trial using hESCs:

> "The evidence to support the clinical trial is that rats get better … and that's about as far as it goes. But that's about as far as it ever goes." (Field notes 01/05/14)

It also means that up until the point of clinical trials there are likely to be a number of fundamental uncertainties about how cell therapies will behave *in vivo*. For

instance, it is often not clear where the cells will end up in the body or what effect they will have, as highlighted by these quotes:

> "We have grounds to believe, rightly or wrongly, that if we put the cells into the tumour rather than into the bloodstream without giving the patients chemotherapy first ... that will minimise the risk of cytokine storm. But you know, we don't know until we do it." (INT5)
>
> "And you don't know where the cells will go, because your animal models won't tell you that." (INT12)

There is also uncertainty about how much the cells will proliferate; for instance, Interviewee 12 described one trial he worked on where there was an average 35,000-fold increase in the number of cells found in the body compared to the number administered, and significant variability between patients. He concluded from this that many cell therapies would not necessarily have a linear dose response, and that clinical testing would need to adapt to this:

> "We're probably going to be looking at thresholds rather than dose per kilo." (INT12)

Dose variability was also an issue for other interviewees, such as Interviewee 14, who explained that the procedure for delivery can have a significant effect of the number of cells that survive (and therefore the effective dose):

> "I've seen grafts where the viability of cells is rapidly decreasing with relation to the bore of the needle even. So the cells basically die due to the sheer stresses of the injection" (INT14)

In another example, Interviewee 1 explained that scientific developments in cell production were expected to change the proliferation potential of the cells, but that until this was tested clinically it was unknown how much effect it would have:

> "We all think … second generation cells are potentially less safe, and that's because they grow more in the patient. So it's slightly illogical, because they say you should start with a very low dose of third generation, but actually if the concern is that they're going to

> expand a lot in the patient then what difference does it make?" (INT1)

Without animal models, then, it appears to be very difficult to generate valid data about a number of fundamental aspects of cell therapies before undertaking first-in-man clinical trials.

Of particular concern here is the difficulty of ascertaining toxicity in an animal model for a cell therapy intended for use in humans. This issue is complicated by the regulator's unfamiliarity with the product, as highlighted by this quote from Interviewee 5:

> "Safety testing of course is very difficult, because we're dealing with a human cell therapy product. And that is all that the MHRA really is interested in - they want to see what work you have done with the proposed therapeutic agent itself. So if you're an immunologist like me, putting human T-cells into a mouse doesn't make a lot of immunological sense really." (INT5)

The key issue here appears to be that safety data from animal models will be less reliable for cell therapies than for drugs because the treatment involves human cells being administered to another animal, as explained by Interviewee 12:

> "Endless numbers of experiments with mice showing it's safe if you put it into a mouse - or worse than that, we have this big tumour in a mouse and we inject these cells and they go to the tumour - well the tumour's a human tumour and the cells are human cells, so you know it doesn't necessarily mean in a human they will go to the tumour and they won't all go to the lung and kill the patient." (INT12)

He went on to reflect that relying on pre-clinical safety data from animal models might actually mask potential safety issues:

> "I think pre-clinical experiments in regenerative medicine and adoptive cell therapies, and all of the ATMPs, are quite often dangerously uninformative. Because they give you a warm woolly

> feeling that makes you feel great, and you get a feeling of safety that's completely unjustified." (INT12)

This quote suggests that animal models might not be merely uninformative for cell therapies, they could in fact be detrimental, because they could give regulators and ethics committees, more used to assessing safety data for drug studies, a false sense of security.

Emerging from this account of uncertainty is a picture of clinical trials taking place in the context of a fluid and shifting scientific base. Stem cell science is much more complex, and currently still much more uncertain, than the science underpinning traditional pharmaceuticals, and the risks involved are potentially much greater. The scientific uncertainties surrounding MSCs that I described are fundamental - in fact they could even be described as existential, in that there is no consensus about what these cells actually 'are'. Such scientific uncertainties exist, to a greater or lesser extent, for all cell therapies currently being developed for clinical use, and in particular for the pluripotent cells that may have the most potential to 'revolutionise' healthcare. Furthermore, scientific research is progressing at a phenomenal pace, which can outstrip the careful clinical testing required to develop a safe and effective treatment. Although scientific uncertainty is not necessarily a barrier to therapies being used in the clinic, as the high number of MSC trials demonstrates, it is nevertheless problematic. My findings show that uncertainties about the characteristics and behaviour of different cell populations make it difficult to accurately predict the risk of a particular therapy, the likelihood that it will be effective, and how to make it more effective. Lack of clarity about the definition and description of cell populations also makes it difficult to compare the results of trials, and to predict how regulators will treat a particular therapy, and the use of the term 'stem cell' raises certain expectations among patients, which may not be aligned with the actual properties of the cells being used.

Linked to, and interacting with, these scientific uncertainties are further uncertainties about how the cells will behave when administered to a patient. These uncertainties, combined with the unpredictability of the manufacturing process (discussed in Chapter 5) and the general complexity of the clinic, means that cell

therapy trials are much more complex and have many more variables to consider than a traditional drug trial. Interviewee 2 highlighted this issue, and alluded to its implications for trial design and long-term product development:

> "To my mind it's not like 'have you got the right drug at the right dose' – there are so many parameters, it's just too complex to get all those parameters right." (INT2)

This quote highlights how difficult it is to isolate specific elements of a cell therapy within a trial, in part because there are so many variables to consider, and also because these variables can interact with each other in unknown ways. For instance, if the cells for an autologous therapy do not expand well in culture this may be due to an underlying problem with the patient's cells, that might or might not be linked to the condition being treated, which then may or may not affect the likely outcome for that patient. It could also, however, be linked to the manufacturing process itself, or could be affected by the way that the cells are administered to the patient, and it could be a combination of all these factors, or of different factors for different patients. Each unknown factor for a cell therapy, then, does not just add to the overall uncertainty, it effectively multiplies it; this makes it extremely difficult to isolate the aspects of the treatment that are successful or unsuccessful, and challenging the concept of a 'controlled' clinical experiment which is at the heart of the randomised controlled trial (RCT) methodology.

6.3 Resolving uncertainty: the key to translation

The findings presented above suggest that clinical and scientific uncertainties are a significant factor in most cell therapy trials, and resolving these uncertainties is clearly crucial if these trials are to lead to successful therapies. Gaps in scientific knowledge are, of course, continually being addressed through laboratory research, but my research suggests that it is likely to be in clinical trials, which form a crucial link between science and the clinic, that the majority of the uncertainties described above will need to be resolved. In this section I will look first at the ways in which scientific uncertainties are addressed through clinical trials, by exploring the concept of 'reverse translation', and I will then go on to look at how trials also help to resolve

clinical uncertainty, as trialists learn from the experience of actually using cell therapies in the clinic. I will also consider how both scientific and clinical uncertainties are reconciled to some extent by the acceptance of a tolerable level of uncertainty, and will show how these conceptions are neither unproblematic nor uncontested.

6.3.1 Resolving scientific uncertainty: "reverse translation"

Although the primary purpose of a clinical trial is to assess the clinical safety and/or efficacy of a particular treatment, it was evident during my fieldwork that the majority of trialists feel that clinical research can also make a significant contribution to the basic science. Interviewee 15 described this as "reverse translation", a phrase that I also encountered in published case study findings (Birchall et al., 2013), and in the trial registry entries for some studies (for instance the RegenVOX trial). Reverse translation is presented as a process whereby as well as scientific knowledge being generated through laboratory research and then applied in the clinic, clinical research is also used as the starting point for generating new scientific knowledge. During my fieldwork I encountered a number of examples of reverse translation happening retrospectively: i.e. a cell therapy had already been trialled in the clinic, and the results either highlighted previously unknown scientific information about the cells or prompted further scientific research to explain the clinical results. For instance, a clinician involved in one of the earliest clinical trials of limbal stem cells explained that it was only after many of the first grafts failed that the team developed an assay to characterise the cells. They discovered that successful patients had been treated with a higher number of stem cells in their graft, and they were then able to undertake further research into the best ways to increase the number of cells produced (Field notes 01/05/14). In another example, Interviewee 7 described the way that scientific analysis of the cells used in an early trial of a T-cell therapy changed the way that these therapies were being developed:

> "The therapy worked on a particular receptor, so then they went back and looked at the cancers and said 'which one of these cancers expressed the receptor?' When they looked at the ones that expressed the receptor that had the treatment, they'd got miles better - and paradoxically the ones that didn't have the

> receptor got worse with the chemotherapy. So going back and stratifying around some aspect they subsequently discovered changed the complete nature of the therapy." (INT7)

Both of these examples highlight how clinical findings can be used to direct scientific research, just as much as basic science is used to develop and refine the treatments tested in the clinic.

Perhaps because of these early experiences of clinical findings helping to contextualise scientific research, some cell therapy trials are now using this approach on a prospective basis: i.e. the trial has both clinical and scientific aims from the outset. The ENABLE trial is perhaps the best example of this approach: the protocol includes not only measurements of clinical safety and efficacy, but also a range of exploratory measures, including histology and imaging. The trial is also aligned with a programme of basic scientific research that characterise the cell populations implanted into patients, providing a better understanding of their proliferation and differentiation potential. Although ENABLE was by far the most comprehensive example of such coordination between clinical and scientific research that I encountered, there were a number of other trials which incorporated some element of basic scientific research. Sometimes this was seen to be a fundamental part of the trial, as was the case for Interviewee 15:

> "When you do a trial like this I think it's your obligation to try to get as much information out of the trial as you possibly can." (INT5)

In other cases, scientific objectives were seen more as a useful addition to the research, rather than being central to the trial:

> "It's fundamentally descriptive, and it wasn't why the trial was set up - it's spin-off basically, it's additional." (INT4)

Whether central or peripheral to the trial, it appears that this type of approach is gaining ground. The ENABLE team explained to me that the MHRA had encouraged them to include such exploratory outcome measures in their trial, and Interviewee 8 (a trial methodologist) noted that this approach is starting to be adopted for many trials:

> "I think we're beginning to have, to have your primary outcomes and secondary outcomes and there might be exploratory outcomes. Which again always gives you a little bit more flexibility of what you might look at." (INT8)

Reverse translation, in the form of exploratory outcome measures, thus appears to be an increasingly common and acceptable feature of cell therapy trials.

Reverse translation clearly has the potential to facilitate innovation in the field by creating more alignment between scientific and clinical research, but it is not without its problems. Exploratory outcome measures require additional data analysis, which can be difficult for research teams who have limited time or resources. A good example of this was the experience of Interviewee 4, who had been keen to collect as much scientific data as possible during the trial, but two years after the trial closed had still not been able to analyse it:

> "We've got some histology results - which as soon as I get the bloody computer programme working I'll analyse - with about 800 or so individual samples." (INT4)

Exploratory outcome measures also tend to require additional procedures, such as biopsies, which can make trials unwieldy - for instance many of the logistical problems I witnessed during my ENABLE fieldwork related to the logistics of arranging biopsies that would be used for scientific research. These biopsies also raised the possibility that the collection of data for scientific purposes could reduce the precision or accuracy of the clinical results. The team were concerned about conducting biopsies too close to the collection of patient-reported outcome measures (a primary efficacy measure for the trial), because of the risk that the biopsy procedure could affect the patient's subjective experience of pain. This issue was particularly complicated because they were uncertain about both the scale of any likely effect and the direction it might take: the biopsy could actually stimulate healing, meaning any improvement in pain scores could be due to the biopsy rather than the cell therapy, or conversely it might cause the patient additional pain, diluting the effect of the cells.

Another potential stumbling block for reverse translation is the fact that scientific research normally requires an understanding of the characteristics of the cell population used in the treatment, in order to be, in the words of Interviewee 4, *"a bit less like black magic".* The drawbacks of failing to characterise the cells were highlighted by Interviewee 12, who explained that it could make it difficult to evaluate trial results:

> "So now we know you don't want to give CD124+ as mesenchymal cells because they won't do what we particularly want them to. Other people might find that that's the population that does what they want to do. But at the moment all the trials that have been done, no-one knows how many CD124+ cells went in, because no-one's measuring it." (INT12)

Here we can see again the pace of change in scientific research outstripping the work being done in the clinic. Exploratory outcome measures offer an opportunity to prospectively address this issue; for instance, one of the exploratory outcome measures for the ENABLE trial involves characterising the cell populations used in treatments and comparing the results to clinical outcomes for patients, thus potentially identifying subsets of cells that have particular clinical utility. Another example of the 'future proofing' work that I described in Chapter 5, this is a way of addressing the conflicting temporalities of scientific and clinical research. It is far from a universal approach, however, and many of the trials currently underway in the UK do not report any work being done to characterise the cell population used. As with the variety of approaches to cell purification that I reported in Chapter 3, this variability reflects a lack of consensus amongst trialists as to the importance of cell characterisation. This is one instance where there appeared to be a distinct division between the clinical and scientific communities, with scientists largely in favour of characterisation and clinicians generally being less concerned as long as the treatment appears to work. One research scientist, discussing the issue at a conference, even stated this division explicitly: *"I think it's [cell characterisation] a really important point academically, but clinically it may be less so"* (Field Notes 21/11/13).

These divergent views on the importance of cell characterisation reflect a wider debate about the amount of scientific uncertainty that is acceptable for a treatment that is being tested or used in the clinic. Interviewee 1 reflected on this issue, explaining that although there was a theoretical risk of toxicity when using an uncharacterised cell population, in practice this is not seen in the clinic:

> "We don't analyse exactly what it is … if there is a mixture, there are some cells that can recognise the tumour but there are some cells that can't. And obviously they could be actually harmful I suppose, possibly, [but] in reality we don't really see any significant toxicity from the cells." (INT1)

As this quote demonstrates, there is a difference between the theoretical risk caused by a lack of scientific knowledge, and a likely clinical risk of toxicity. Likewise, many researchers did not feel that a full understanding of the basic science is necessarily a prerequisite for efficacy; for instance, when discussing the use of MSCs for GvHD, Interviewee 6 said:

> "Well the biology is probably still unknown to some extent. The only thing that I know is that they work brilliantly in a lot of patients." (INT6)

In another example, a clinician involved in early clinical trials of a tissue engineered therapy explained that the success of the first operations showed that experimental technologies with badly understood science can work well in the clinic; he concluded from this that *"translation doesn't require perfection"* (Field notes 01/05/14).

In positioning scientific uncertainty as an acceptable, and even inevitable, aspect of translation, some trialists drew parallels between experimental cell therapies and more established cell transplantation treatments. For instance, Interviewee 12 described the uncertainties that still surround islet cell transplants, despite their routine use in the clinic:

> "We did the first ever islet cell transplant in the UK here in 2004 - I can't tell you that all the patients who've subsequently had an islet cell transplant had the same islet cell product. But I can tell you -

> without any real evidence - that that is definitely not the case, certainly the dose that they've been given is all over the place. And yet patients have benefitted from those islet transplants.

He went on to link this to the situation with cell therapies, drawing parallels between the uncertainties involved, and how they should be treated:

> "Organ transplantation already occurs, and we don't have a release criterion for each organ that we give apart from that it's not infectious and that it's got a blood supply. And that's going to be true of many of our products, but it doesn't necessarily mean that we shouldn't be doing it." (INT12)

Aligning the uncertainties of experimental cell therapies with existing, accepted forms of treatment is thus a way of positioning a certain level of scientific uncertainty as acceptable in the clinic.

The acceptance of uncertainty in cell therapies based on their similarities to organ transplantation is not a universally-held opinion. For instance, during a discussion at a tissue engineering conference, one cell scientist expressed the view that if cells are going to be put in patients it is important to be able to identify and track them (Field Notes 21/11/13). Another scientist countered this by saying *"but we've been doing bone marrow transplants for years, and we don't know what's in them."* Rather than accepting this argument, the first speaker responded that perhaps this was also a problem, and that rather than accepting a similar level of uncertainty for cell therapies, the aim should in fact be to learn more about bone marrow transplants. A further perspective was then added by another speaker, who argued that regardless of whether cell characterisation was necessary from a clinical or scientific perspective, it was likely to be a regulatory requirement in future. Clearly, then, there is no consensus about the amount of scientific uncertainty that is acceptable for a cell therapy to be used in the clinic, whether because of ethical, regulatory or academic considerations.

6.3.2 Resolving clinical uncertainty: learning through doing

I described earlier in this chapter the various clinical uncertainties pertaining to cell therapies, which include factors relating to patients and disease epidemiology, as well as the manufacture and action of the cell therapies themselves. Although the nature and extent of these clinical uncertainties will vary between treatments, common to all of them is the fact that they cannot be resolved *in vitro* or in animal models. Because cell therapy uncertainties relate to the way human cells behave when administered to a human, they can only be resolved through clinical testing, as Interviewee 12 emphasised:

> "The best test model is a human, if it's a human who has the potential to benefit from it." (INT12)

The importance of testing cell therapies in patients, which was raised by most interviewees, is encapsulated in this quote from Interviewee 5 (who was involved in a first-in-man study of an innovative gene-engineered cell therapy):

> "My philosophy also is that this is really really new - so you know it's all well and good sitting here talking about what you're going to do, but none of us has done it as yet, or very few of us have. And we will learn by the experience of going through the process … the patients are going to teach us the lessons in essence." (INT5)

One of the most important lessons that can be learnt from patients involves understanding more about the variety of responses to the treatment, as described by Interviewee 15:

> "What that involves is a more detailed understanding of the patient, then they're given therapy, and then a more detailed understanding of what happens after the therapy - not just efficacy." (INT15)

In a similar example, Interviewee 2 explained that his trial would be used to determine the optimum patient characteristics and delivery procedures for cell transplantation, so that once a stem cell treatment was developed the clinical uncertainties would already have been somewhat resolved:

> "You've got the patient cohorts, you've got the interactions with the drugs, you've got all the immune biology sorted out. So that when the time is right for the first generation of really viable stem cell based cells to come through, one can go to the clinic." (INT2)

Clinical testing is also an opportunity to learn more about the disease, for instance Interviewee 9 explained that as well as looking at the treatment itself, his trial was also designed to look for disease indicators that would provide a benchmark for how well the treatment had worked: *"we're looking for biomarkers as we go along."*

As well as providing an opportunity to learn more about the patients and diseases to be treated, clinical testing can also help to resolve uncertainties about how cells will behave *in vivo*. For instance, Interviewee 5 described how they were using a clinical trial to find out whether cells injected directly into a tumour migrated to other areas of the body:

> "We will be using flow cytometry to see if any of the cells leave the tumour and are detectable in the blood, because of course that could have clear relevance to toxicity." (INT5)

A similar approach was being followed by Interviewee 9 - although, as with some of the exploratory scientific outcomes that I described above, this was added almost as an afterthought once the trial had started:

> "We're about to put in an amendment to our protocol now where we're going to radiolabel the cells to see where they go." (INT9)

Understanding more about how cells behave *in vivo* is not only useful for evaluating toxicity, it can also improve efficacy by helping cell therapy developers learn more about the optimum treatment protocol. The importance of the information gleaned from clinical testing was emphasised by Interviewee 11, who explained that the difficulties of testing cell therapies in the clinic made it challenging for his company to refine their product in terms of the dose and timing of treatment:

> "Obviously it's a little harder to do that kind of stuff in humans … you can't do the normal kind of Phase 1 type work to look at the best dose response. So that's been a little bit of a challenge for our

> company, you know - are you giving enough cells, what's the optimal dose, what's the optimal timing." (INT11)

It seems, then, that trials are perceived as a means of addressing the limitations of animal models for cell therapies that were discussed earlier in this chapter, by providing an opportunity to learn about how cells behave when administered to humans.

Another important benefit of clinical testing is that it allows developers to learn more about the logistics of delivering a cell therapy. Interviewee 17 described his trial as an opportunity not only to test the safety and efficacy of the treatment, but also to refine the process of manufacturing, storing and delivering the cells:

> "What goes wrong, what goes right, the logistics of supply, and keeping things alive while the patient's there." (INT17)

The importance of understanding the logistics of actually delivering the treatment is reflected by the fact that many of the trials included in my dataset stated some type of feasibility analysis as one of their secondary objectives. For instance, the AutoDECRA trial measured the success rate of the cell manufacturing process, based on the proportion of patients entering the trial for whom it was possible to produce enough cells of sufficient quality, and also the acceptability of the treatment protocol to patients. Clearly these uncertainties could not be addressed through either animal models or laboratory testing, so a clinical trial is the only opportunity to resolve them. In some trials the logistics of delivering the cell therapy is even a primary outcome, as was the case for Interviewee 1, who was trialling a therapy for which safety and efficacy had already been established:

> "We've developed it locally, and it is an issue as to whether we can transport the cells and treat patients elsewhere. And one of the main aims of our EU trial is to test exactly that." (INT1)

These examples suggest that clinical trials of cell therapies, unlike drug trials, are important not only for testing the safety and efficacy of the treatment, they are also an important opportunity to make cell therapies more practical and cost-effective, which is likely to significantly improve the chances of clinical adoption.

Clinical testing thus appears to have an important role in developing safe, effective and practical cell therapies. Crucially, it appears that this process is an incremental one; in order for treatment protocols and practical logistics to be refined, it is essential that learnings from clinical testing can be used to inform further development of a cell therapy. This is often recognised in the reports of early trials, such as this example from the SIAMMS-II trial: "Optimisation of treatment is likely to be an *iterative process* dependent on efficient *back-translation* of information gained from carefully designed clinical trials" (Rice et al., 2015, p.5). Notably, the report uses the phrase 'back-translation', suggesting that the process of resolving *scientific* uncertainties by working backwards from clinical effectiveness can also be applied to resolving *clinical* uncertainties. The emphasis on the process being iterative is also important: this term was used extensively by the trialists I interviewed, emphasising their need to make incremental refinements and adjustments to the treatment as new information is accumulated. The way this happens during the trial process is highlighted by this quote from Interviewee 7, describing an early-phase gene therapy trial he had been involved in:

> "They took three patients, gave them a small dose, then took another three patients, gave them three times the dose, then they took another three patients, gave them five times the dose. Then they changed the delivery system so they could get better delivery, then they did six patients. So it's an iterative process." (INT7)

The ability to move forwards incrementally, making changes and adaptations based on the experience of using the treatment, thus appears to be an essential aspect of reverse translation.

The importance of being able to make changes based on the experience of actually treating patients was reflected in the process described by Interviewee 17, who emphasised the importance of learning from a small number of compassionate use cases before moving on to a trial:

> "They're very valuable … bringing the surgical or science community along with the technology rather than keeping it secret til you get to a clinical trial, and then everyone's asking questions

> because they haven't seen it before. And by publishing those things you get feedback about things that you hadn't thought about, or things that are maybe more valuable that you can start to incorporate. So in a way you use the community to help you refine the product." (INT17)

This quote is particularly interesting because Interviewee 17 was a commercial developer, and, as I discussed in Chapter 4, there is a perception that companies are unwilling to develop treatments in a transparent and collaborative manner. However, it appears that in this case the company was actually keen to have the opportunity to gain experience of using a treatment in the clinic in order to share knowledge and refine the treatment, before moving on to more commercially-sensitive trials. This emphasises how important the process of iterative development is to cell therapy innovation, and again is in distinct contrast to drug trials, where there is little need (or willingness) to share knowledge during the development phase.

It appears, then, that as well as providing an opportunity to generate data that furthers scientific understanding, iterative clinical testing is crucially important for developing a usable, commercially-viable cell therapy. This process of refinement is challenging, however, in a clinical trials framework which is very restrictive in terms of how much the treatment can be changed once clinical testing has begun. This clash between the iterative process of innovation and the linear clinical trials framework is one of the crucial differences between drug trials and cell therapy trials, as explained by Interviewee 9:

> "It's iterative, it's really an iterative process. And that's not like drug discovery, because usually what you're giving in Phase 1 will be the same as what you give in Phase 3" (INT9)

The process of trialling cell therapies is also challenging because the very novelty of the treatments means there is very little accumulated knowledge and expertise about how to trial them, and of the specific feasibility issues these trials present. Each trial thus becomes not only an opportunity to learn about and refine a specific treatment, but also to learn about cell therapy trials themselves, as Interviewee 5 explained:

> "In my opinion, you can't learn how to do a clinical trial of a cell therapy from writing a clinical trial protocol or an IMPD - you've got to actually go out and do it. Because there's nobody's going to teach you, so you've got to learn - because it's being done for the first time, you've got to learn from experience." (INT5)

Interviewee 5 went on to explain how he would approach another trial differently, suggesting that the concept of learning thorough doing applies not only to using the treatment but also to running the trials themselves:

> "Even already at this stage, before having treated the first patient, there are things, many things we would do differently if we were starting this trial now." (INT5)

Although there are clearly benefits to this accumulation of trials knowledge, it also presents a significant barrier to translation, because until each centre running trials has developed sufficient expertise it is likely that the trials that take place will not be as efficient or as informative as they might be. The localised, site-specific nature of much cell therapy development (discussed in Chapters 3 and 4) suggests that there may be barriers to the sharing of accumulated knowledge about trials, and certainly there was limited evidence in my interviews of this happening on a routine basis.

A further limitation to the way that clinical testing can, or should, be undertaken relates to the management of risk. As I discussed in Chapter 4, clinical research involves a delicate balance between the risk to individual patients on the one hand and the potential benefits for many future patients on the other. Given that clinical testing appears to be particularly important for the development of cell therapies, it was interesting that my interviews identified a range of attitudes towards the level of risk that is acceptable in such testing. Many interviewees advocated a cautious approach, as exemplified by these quotes:

> "I always say, when we come to stem cell based therapies for [disease] the first patients will be almost deliberately under-treated, because it needs to be safe. And that's how we'll move forwards." (INT7)

> "I didn't want to put people into this horrendously dangerous treatment without good thinking about it." (INT4)

Other interviewees described less risk-averse perspectives, such as Interviewee 1, who had himself used a cautious approach in his trials by using a very low dose to start with, but described a US centre that had a very different view:

> "They've always taken the approach that you should produce as many as you can and give them back. And, well they've had a couple of spectacular deaths, arguably as a result of that approach, whereas we, well the trial we did was at a quite cautious level, dose escalating, getting there, treat 17 patients and then we found there was toxicity when we got to the highest dose - nobody died but it was clearly toxic." (INT1)

Interestingly, Interviewee 7 felt that a slightly less risk-averse approach could in some cases be more aligned with the priorities of patients, who might be prepared to accept a greater level of risk in order to have early access to a promising new treatment:

> "The patients are probably much happier to take a risk at a much earlier stage in development for the gain that they may get - it's obviously very individual but often they will." (INT7)

It seems, then, that views on acceptable clinical uncertainty in a trial are very individualised, and this inevitably conflicts with the ethical approval process for trials, which imposes an external evaluation of acceptable risk on both patients and clinicians alike.

The quote from Interviewee 1 above highlights how different approaches to risk can affect the speed with which clinical uncertainties can be resolved, and he went on to reflect on which approach was better. Whilst he clearly felt more comfortable with a cautious strategy, he could also see the benefit of accepting a greater level of risk in order to resolve clinical uncertainty more quickly:

> "When I spoke to the guy who's the head of the [other centre] and said 'well isn't our approach better', and he sort of says 'well no

> you've spent 2 years treating 17 patients and if you'd just put a large dose into the first patient you'd have known after one patient.' Yeah, which you know arguably - you could argue it either way." (INT1)

Interviewee 12 also reflected on this theme, considering the example of a previous compassionate use case which had resulted in the death of the patient:

> "The surgeon involved said 'I really wish I'd never done this, we really have to think about whether we do this again'. And the cardiac transplant surgeon at [hospital name] said for God's sake grow up - have you any idea how many heart transplants we did before the first one worked? If anyone had said 'well I've only done two of these and 50% of them died, I'm not going to do another one' it would never have happened." (INT12)

This quote emphasises how different individual perceptions of risk can be, but also highlights to some extent the *disciplinary* divisions, with surgeons involved in an area that has a history of risky human experimentation leading to life-saving treatments being perhaps more willing to accept this as part of the process. As I discussed earlier, many interviewees saw parallels between cell therapies and surgical techniques, in particular organ transplantation, in terms of the process required to hone the treatment. However, organ transplantation was pioneered in a much less restrictive clinical research environment, and even now surgical techniques are much less likely than drugs to be evaluated in RCTs. This disconnect between the regulatory framework and the development process for new treatments is seen to have the potential to severely restrict innovation, as highlighted by this quote from Interviewee 12: "*If organ transplants had been regulated as medicines, we wouldn't be doing organ transplants.*" Again, this is a marked contrast between cell therapies and drugs, and the balance between protecting patients and the need to resolve clinical uncertainty through human testing will clearly be an important and contentious issue for the future of the field.

6.4 Discussion

These findings suggest that cell therapy trials are being used not only to address the traditional questions of safety and efficacy, but also to resolve clinical and scientific uncertainties in the treatments. Inevitably, given the translational agenda, the questions that are being asked in basic scientific research are in fact to some extent clinical questions, and ultimately relate to how cells will behave in the human body. I argued in Chapter 1 that rather than being one-dimensional physical objects, stem cells must in fact be considered in three dimensions: physical, temporal and spatial. The physical dimension, and to some extent the temporal, can be researched *in vitro*, but the spatial dimension (i.e. the properties and behaviour of the cell in relation to the specific micro-environment, or niche) can only accurately be researched *in vivo,* and given the limited applicability of animal models this means clinical trials in humans. A good example of this is the fact that it is only through clinical testing that the difference between a mixed and a purified population of cells can be assessed, because the interaction of these cells with the surrounding cells will affect their behaviour, and therefore therapeutic impact. The importance of testing in humans is further increased by the additional uncertainties of the clinic: for instance, the wide variation in patient response that has been seen for some treatments, which is likely to be caused by a mixture of patient/disease-related factors and factors relating to the cell product used. Clinical trials also appear to be an important opportunity to refine manufacturing and delivery processes, which are essential elements of a successful therapy, and fundamental to the translational process.

As well as using clinical research to resolve uncertainties, trialists also appear to reconcile uncertainty by making arguments for an 'acceptable' or 'inevitable' level of scientific uncertainty in the clinic. My results also show, however, that there are conflicting views on how far such uncertainty can or should be accepted. The positioning of cell therapies as akin to organ transplants is an interesting case in point: for some, the successful development of transplantation in the absence of scientific certainty creates a model for the development of cell therapies, and an ethical justification for accepting scientific uncertainty in the clinic. This experimental approach to clinical development can be seen in the model of innovation for

surgical methods, for instance hip replacements (Metcalf and Pickstone, 2006), and proponents of this approach highlight the development of HSC transplantation as an example of iterative clinical experimentation, rather than basic scientific research, leading to a therapeutic breakthrough (Martin et al., 2008). For others, however, the development of transplantation is a cautionary tale, because of the number of people who died during the early years because the underlying science was poorly understood (Daley, 2012). Daley also questions the contention that such experimentation is necessary because successful treatments such as HSC transplantation would not have been developed without it, arguing instead that HSC transplantation would simply have taken longer to emerge but would have avoided the high mortality seen in the earliest experiments. The surgical innovation model also gives individual clinicians significantly more autonomy than the more regulated pharmaceutical trials process, and the risks this creates are highlighted by this BBC report on the Macchiarini case: "a doctor *persisting with a technique* that showed few signs of working and *able to take extraordinary risks* with his patients, and a medical institution so attached to their star doctor that they *ignore mounting evidence of his poor judgement*" (BBC, 2016). This raises important concerns about institutional oversight and clinical autonomy, and also highlights a fundamental tension at the heart of cell therapy translation: clinical research may be essential for resolving uncertainties, but these uncertainties potentially make clinical research unacceptably risky.

Despite this tension, it is likely that cell therapy trials will continue to take place in conditions of significant clinical and scientific uncertainty, and will in fact play a vital role in resolving them, as they are interlinked and thus can only be addressed through coordinated, recursive research. This challenges the argument for cautious translation, which assumes that scientific uncertainties can largely be resolved separately from clinical uncertainties, both spatially (i.e. in the laboratory) and chronologically (i.e. before clinical uncertainties are addressed). The tension between these two perspectives can be understood in the context of different understandings of the innovation process itself: cautious translation can be seen as aligned with a technologically deterministic model of innovation, whereby there is a

linear path from laboratory research to the invention of a new technology and then to its eventual adoption by users. From this perspective, technological innovation takes place separately from the context in which it is used, and this is reflected in typical representations of translational research, which assume a 'bench to bedside' process whereby advances in scientific research are made in the laboratory and then 'translated' into effective treatments for the clinic (Godin, 2006). STS accounts, however, have challenged this linear model by arguing that rather than being technologically-determined, innovation is in fact a recursive, highly contingent process of stabilisation and closure (Bijker, 1993). New technologies are thus shaped by the social and institutional contexts in which they are developed, and user involvement in the innovation process is a critical factor in the way a technology develops (see for instance Morlacchi and Nelson, 2011; Nelson et al., 2011). The reverse translation and learning through doing approaches to resolving uncertainty described in this chapter are clear examples of this iterative, contextualised model of innovation, and emphasise the fact that a recursive, rather than linear, relationship between bench and bedside is fundamental to the translational process.

Although this combined approach to scientific and clinical research, which might be thought of as 'bio-clinical' trialling, provides a means of reconciling the tension between cautious translation on the one hand and the recursive nature of innovation on the other, my results suggest that such research can face a number of obstacles. Collecting scientific as well as clinical data increases the administrative demands of a trial, and a lack of resources is of course already one of the key challenges facing cell therapy trials. It is unlikely that the scientific potential of clinical trials can be fully realised without adequate funding, but we saw in the previous chapter that funding bodies tend to distinguish between 'basic' and 'translational' grants, and are reluctant to fund too much basic science in a clinical study. Current reporting practices can make it difficult to evaluate and compare the scientific aspects of cell therapy trials, and the collection of scientific data can also increase the burden on patients, and could even compromise the validity of clinical research. This creates an additional dimension in the research vs. care dynamic, with potential conflicts not only between the care of the patient and the needs of the clinical

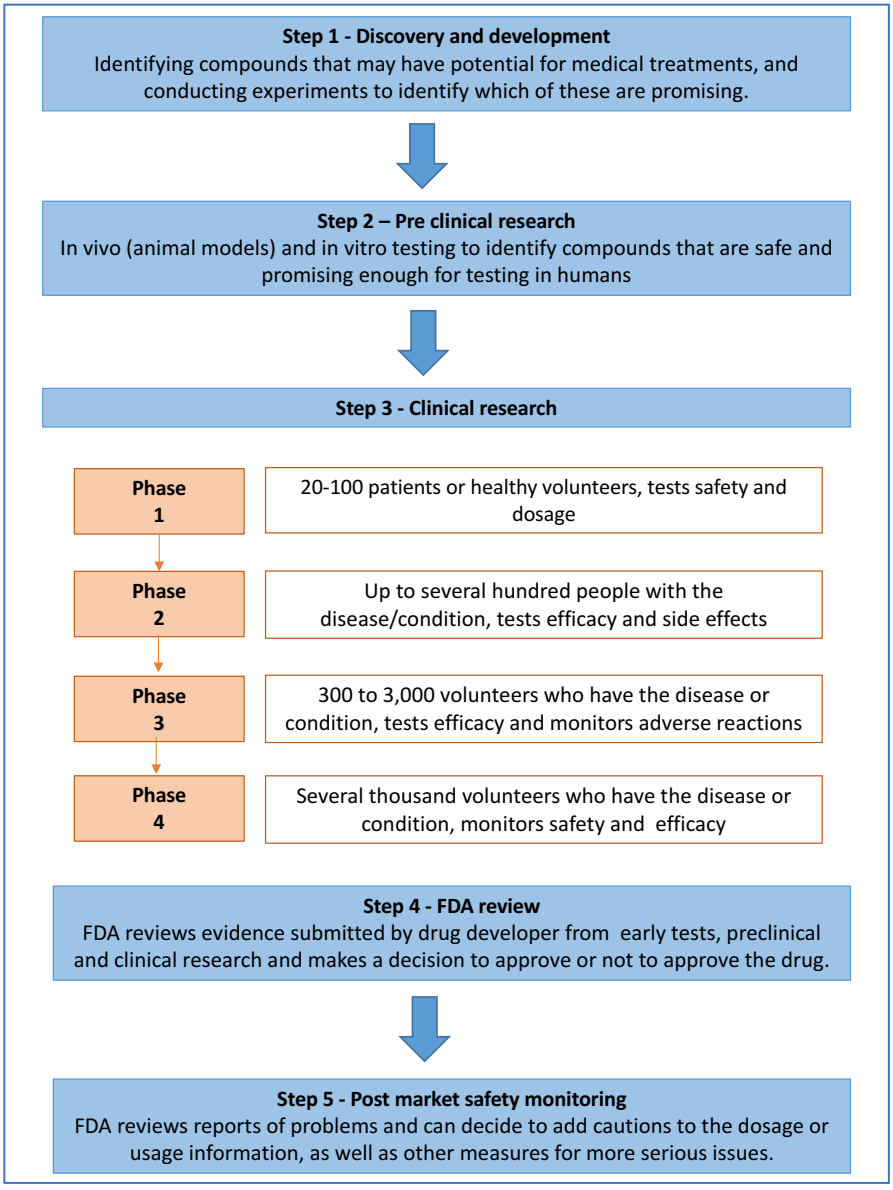
research, but also between both of these and the needs of the scientific research. The full support and engagement of clinicians will clearly be vital, and thus bio-clinical trials will require much closer collaboration between clinical and scientific researchers than is traditionally the case, reiterating the importance of interaction between different domains that I discussed in the previous chapter.

The importance of clinical and scientific researchers working together closely is emphasised in much of the literature on cell therapy translation. Keating (2012) argues that "success is more likely if clinician investigators work very closely with laboratory researchers to design better clinical trials", and Lindvall (2012) claims that the key to translation of stem cell therapies for CNS disorders is better communication between clinicians and scientists, because as well as being able to develop the right cells, it is also necessary to be able to select the right patient and know the best site for delivery. Likewise, Foley and Whitaker (2012) highlight the importance of companies and clinicians collaborating more effectively because they have different areas of expertise, in the manufacturing process and clinical procedures and pathways respectively, which are equally important in the success of a novel therapy. My findings certainly support this position, with the uncertainties of cell therapy trials being a combination of clinical, scientific and manufacturing factors. However, achieving successful collaboration between these areas is often hampered by acknowledged tensions between clinicians and biologists (Martin et al., 2008). These tensions result from a wide range of factors, including the diverging goals of medicine, which aims to treat patients, and science, which aims to accumulate knowledge, and significant differences between the two domains in terms of culture, accountability, funding and conceptualisation of risk (Cribb et al., 2008). For cell therapies, one of the key areas of discord is likely to be around the acceptable level of uncertainty in the basic science; this is particularly highlighted by the lack of consensus about the importance for cell characterisation, which is an essential element of reverse translation, and which clinicians tend to prioritise less than scientists.

As well as the challenge of aligning the work of clinicians and scientists, my findings also suggest that a bio-clinical approach to trialling cell therapies is also likely

to come into conflict with the technologically deterministic understanding of innovation which is embedded in the linear phase system of drug development and clinical trials, summarised in Figure 6.3.

Figure 6.3: Phase model of drug development and trials (adapted from FDA, 2017)



Under this model, laboratory research and animal models form the initial stages of innovation. Once these are complete, a treatment moves through the phases of clinical research, from first-in-man Phase 1 trials to confirmatory Phase 3 trials. Once a therapy has entered this framework there is very little scope for altering it, because the results of each trial are based on the specific treatment being tested, and any significant changes thus exclude these results from being used to justify moving on

to the next phase. Clearly this poses a significant challenge if the trial itself is being used to understand more about the treatment, with a view to making changes and improvements. This challenge can be understood in the context of the difference between the development of cell therapies and the drugs on which the phase model was based. A high failure rate is effectively 'built-in' to the evidence-based medicine framework, with up to 70% of early-phase drug trials failing (Daley, 2012). This is because when the modern phase system for trials was developed, Phase 1 was intended as a screening stage, whereby a large number of compounds could be tested quickly and with minimal risk, identifying those that showed enough promise to warrant further investigation (Keating and Cambrosio, 2012). This model, designed for relatively simple chemical compounds, is clearly problematic for the much more complex living tissue involved in cell therapies, with a multitude of variables that could affect the eventual outcome. This suggests it may be necessary to explore alternative research frameworks for cell therapies that can address both the expectations of EBM and the distinctive characteristics of these advanced, complex treatments. The next chapter will look in detail at different perspectives on evidence, providing insight into how such an alternative framework might be achieved.

7. Evidence and expertise: "how much can you leave out and still have an RCT?"

The tensions in the translational research agenda discussed in the previous chapter can to a certain extent be understood as a clash between a scientific research culture based on an experimental model and a clinical research culture which is to some extent rooted in a 'trial and error' approach (Wainwright et al., 2006). Evidence-based medicine (EBM) claims to bridge this gap by applying the rigour of scientific experimentation to clinical research, and it is this concept that underpins the argument that if experimental cell therapies are to be used in the clinic this should be in 'robust' clinical trials. Implicit in this argument is that certain types of evidence are more valid than others, as demonstrated when Daley explicitly spells out the characteristics of 'valid' and 'invalid' evidence: "We also need to design *rigorous*, *blinded*, and when possible *randomised* trials where evidence for clinical efficacy can be defined precisely, rather than depend upon *anecdote* and *clinical observation* alone" (Daley, 2012). Daley's emphasis on randomisation and blinding, and his dismissal of clinical experience, reflects the current orthodoxy of EBM, and his concern with rigour has recently been given greater salience in the field of cell therapy by the publication of research suggesting that the efficacy of some treatments has been overstated by 'low quality' trials (Rosen et al., 2014; Nowbar et al., 2014). Conducting 'high quality' cell therapy trials can be problematic, however, as highlighted by a clinician involved in one of the first UK trials using hESCs when he gave a talk to other clinicians considering running similar trials (Field notes 01/05/14). He explained that the feasibility of a trial will depend on the design, particularly in areas where recruitment is likely to be an issue, and he reflected that this raises an important question: *"how much can you leave out and still have an RCT?"*

There appears, then, to be a fundamental tension at the heart of the trials process for cell therapies: the generation of 'quality' evidence can be at odds with the practicalities of conducting a trial, and indeed with the evidence the trialists themselves need in order to develop the treatment. This chapter explores this issue

of evidence in detail, firstly by looking at how trialists themselves understand the evidence generated by trials, and in particular outcomes measures (which the House of Lords report identified as a key challenge for cell therapy trials), and then by exploring how evidence is understood and used at an institutional level. Before this, however, I will review what I term the 'epistemic' critique of EBM, which provides a useful analytical framework for the empirical discussion that follows. This critique, which draws on literature from a range of disciplines, extends the discussion in Chapter 4 about the mutability of trials by examining the way that EBM defines and deploys the concept of evidence itself.

7.1 An epistemic critique of EBM

Despite achieving hegemonic status, there is no universally-accepted definition of exactly what EBM is or what it entails. The original propositions largely focussed on EBM as a clinical decision-making tool, with the focus being on encouraging the use of systematic empirical evidence when making clinical decisions, and equipping doctors with the ability to critically appraise clinical research. Over time, however, the focus began to move away from individual clinical decision making towards the appraisal and dissemination of the evidence itself, a trend exemplified by the establishment of a number of organisations dedicated to this purpose, such as the Cochrane Collaboration and the Centre for Reviews and Dissemination (Borgerson and Bluhm, 2005; Daly, 2005). EBM principles are now embedded within regulatory processes: for instance most regulating authorities require evidence of efficacy from clinical trials before licensing new treatments (Dehue, 2010), and there is a proliferation of EBM-informed clinical guidelines and care pathways which, to a greater or lesser extent, dictate individual patient care (Will and Moreira, 2010). EBM principles also affect research funding structures and the publication of research findings (Borgerson, 2005; Grossman and Mackenzie, 2005; Edwards, 2007), and have fed into the expanding field of Health Technology Assessment (Webster, 2004).

Linking and underpinning all of the different aspects of EBM is a fundamental principle that the 'best available clinical evidence' should be used to inform clinical decisions. Central to the EBM model, therefore, is the concept that there are various

potential sources of evidence, and that some types of evidence should be considered more reliable than others. At its broadest level, evidence has been defined within EBM as "any empirical observation about the apparent relation between events" (EBM Working Group, 1992). Within this could be included experimental studies such as clinical trials, observational studies such as case control and cohort studies, and unsystematic observations such as clinical case studies and accumulated clinical experience (Bluhm, 2005). One of the most important functions of EBM has been the introduction of hierarchies which stipulate the relative importance that should be placed on each of these different types of evidence. Such hierarchies invariably place randomised controlled trials (RCTs) and systematic reviews of such trials at the top, with non-randomised (or observational) studies lower down, and non-systematic evidence such as case studies forming the lowest tier of evidence (Straus and McAlister, 2000; Bluhm, 2005). Theoretical knowledge, such as that generated by laboratory experiments, is largely excluded, as is clinical experience or 'expertise'.

The primacy given to randomised trials means that to some extent the term EBM has become "synonymous with medicine based on results of RCTs" (Dehue, 2010). This interpretation, which has been described as a 'crude' application of EBM principles (Brody et al., 2005), has been challenged from the beginning by EBM proponents, who have emphasised the importance of using various forms of empirical evidence, in conjunction with clinical experience, to make decisions about the treatment of individual patients (Straus and McAlister, 2000). Although this suggests that the EBM model is in theory open to a relatively nuanced approach to evidence, this type of interpretation has in fact been largely limited to academic discussion in journals. In practice, the increasing use of evidence hierarchies and clinical guidelines often creates a form of 'mechanistic objectivity' (Cambrosio et al., 2006), which leaves little room for flexibility or interpretation. In practical terms, therefore, the main impact of EBM has been to raise the RCT to hegemonic status within healthcare research at the expense of other forms of evidence.

EBM doctrine presents the RCT method as providing the most reliable evidence of safety and efficacy, based on the premise that it is the most 'scientific' method. The narrative is a relatively simple one: randomisation, blinding and

contemporaneous control groups are necessary and (largely) sufficient for generating objective, valid evidence. These key elements demarcate the method as *interventional* rather than *observational,* and this distinction is used by advocates to characterise RCTs as scientific experiments that allow for causal inferences to be made, in contrast to observational studies that can only identify correlation (Torgerson and Torgerson, 2008). Terms such as 'controlled', 'blinded' and 'statistical' create a rhetoric that emphasises scientific credibility (Edwards, 2007; Marks, 1997), as does a reporting style which increasingly mirrors that of scientific research - in particular a focus on the reporting of process, confirming that key steps were carried out in order to create credibility with colleagues. In this way, the RCT is positioned as having the rigour and objectivity of scientific research (Marks, 1997; Simpson and Sariola, 2012), and it is this claim, pursued with "a zeal that at times resembled a religious conviction" (Daly, 2005), that has underpinned the success of EBM. Historical accounts, however, show that in the early days of clinical research there were various schools of thought on the best methods to adopt, and that individuals, social contexts and political processes were extremely important in determining what would eventually be considered the best method (Marks, 1997; Edwards, 2007; Dehue, 2010). In this context, the objectivity of RCTs must be understood not as a scientific fact, but rather as a socially-constructed consensus that resulted from the specific set of circumstances, challenges and power dynamics that were in place at the time that the methodological processes were being developed.

Scholars from various disciplines have challenged the primacy afforded to RCTs, raising questions about the internal and external validity of the method and questioning the argument for its superiority over other forms of research. Some of these critiques, often emanating from history and philosophy of science, challenge the presumption that randomisation is necessary for preventing bias, and therefore the only way to generate valid evidence of efficacy. According to this argument, other methods can be equally effective at preventing selection bias and addressing confounding variables, particularly in trials with small samples (Grossman and Mackenzie, 2005; Worrall, 2007). Worrall challenges the contention that randomisation is necessary for achieving scientific objectivity, citing the point

sometimes raised by Bayesian statisticians that randomisation is rarely used in physics, which many would consider "the most successful science we have". He highlights the fact that most treatments currently in use today have never been subject to an RCT, and yet there is no reason to suppose that the majority of medicine as currently practiced is ineffective. Proponents of EBM tend to claim that the importance of randomisation is 'proven' when a treatment that has shown effectiveness in observational studies shows no significant effect in an RCT (Torgerson and Torgerson, 2008). This assumption is reflected in Daley's (2012) argument that cell therapy research should be limited to 'high quality' randomised studies: "the history of even legitimate medical practice is rife with examples of instances whereby trust in medical intuition alone, or reliance on uncontrolled retrospective or purely observational studies, has led to mistaken presumptions about medical efficacy, only to be corrected when rigorous blinded, randomised trials proved our presumptions to be false." As Grossman and Mackenzie (2005) point out, however, this argument relies on the circular logic of assuming that it is the RCT results, and not those from other studies, that are 'true', whereas in fact other factors could have led to the difference in results (as indeed must be assumed when two different RCTs show different results for the same treatment).

These critiques of randomisation can broadly be described as concerning the internal validity of the method: i.e. the extent to which it measures what it claims to measure. Concerns have also been raised about the external validity of randomised trials: i.e. to what extent can the results of an RCT be extrapolated to a wider population? Worrall argues that the process of randomisation on its own does not exclude the possibility of other factors affecting trial outcomes, or eliminate the need to consider the results in the context of other background knowledge. He points out that there are numerous cases where a treatment was shown to be safe or effective in trials but then showed different results when adopted into general medical practice. Cartwright and Munro (2010) argue that there is a trade-off between internal and external validity: randomisation improves internal validity by accounting for unknown confounders, but because the confounders are unknown there is no way of predicting how representative the trial is of the target population. Part of the

problem with external validity is that RCTs produce overall results which average out different responses in different individuals (Dehue, 2010), and whilst this may be useful for public health decision making, it is of little use to individual clinicians who need to know how a treatment is likely to affect a specific patient (Feinstein, 1995). The failure of RCTs to identify the extent of individual differences in response also hampers the extrapolation of results to different populations, and does nothing to further understanding of what causes these differences (Bluhm, 2005).

It appears, then, that there is a convincing case for randomisation being neither a necessary nor a sufficient condition for generating valid evidence of efficacy, which raises questions about the primacy EBM affords to RCTs at the expense of other forms of evidence. Grossman and Mackenzie (Grossman and Mackenzie, 2005) argue that there can be no justification for viewing RCTs as the 'gold standard', as this implies that the method will be the best in all circumstances, whereas in fact there are many situations in which other forms of evidence might be more appropriate. Likewise, the EBM approach tends to promote RCTs over other methods regardless of quality, so that for instance one small RCT with poorly chosen outcome measures would theoretically be given greater weight than a number of large, well-designed observational studies. Others have highlighted the fact that some safety issues may only come to light through individual case reports, and are therefore likely to go unrecognised in the EBM model which places very little value on such research (Smith, 1996). More 'sophisticated' advocates of EBM might reject this reliance on RCT evidence 'at all costs' (Brody et al., 2005), but in practice the assumption that RCTs are always better than other forms of research persists, despite widespread recognition of variability in quality which is acknowledged to affect validity.

In addition to concerns about the primacy afforded to RCTs, critics also argue that EBM has been slow to acknowledge and engage with the inherent subjectivity involved in using evidence (whether from RCTs or otherwise) to make clinical or policy decisions. The increasing influence of EBM has had significant implications for the treatment of patients, both directly, by affecting individual clinical decision making, and more indirectly through its influence on health policy, reimbursement processes, health technology assessment and clinical guidelines. Underpinning this is an

assumption that objectivity is achieved through basing these decisions on 'evidence' rather than experience or judgement, and that eliminating personal opinions and politics is the best way to achieve consistent and efficient treatment. In reality, however, evidence can be interpreted in various ways depending on the experience, beliefs and values of those doing the interpreting. Unsurprisingly, therefore, the use of RCT results in decision making is often affected by personal and professional agendas, and the supposedly objective 'evidence' can become a device used to construct a claim of scientific validity for a particular course of action (M. Edwards, 2007). A recent study of home birth (De Melo-Martín and Intemann, 2012) presents an interesting example of how the same evidence can be used to promote different policies depending on the pre-existing beliefs of those interpreting it. Although the evidence on home birth is mixed, there is a general consensus that it reduces the risk of an instrumental delivery, but that there may be a slightly increased risk of infant mortality. Proponents of home birth tend to be those who wish to reduce the medicalisation of childbirth, and who therefore see the reduced risk of intervention as a considerable benefit which outweighs a small (and unproven) additional mortality risk. Conversely, proponents of hospital birth place less importance on reducing the risk of intervention, and prioritise the fact that some studies have shown a slightly increased mortality risk. Thus, each side takes the same evidence but interprets it differently depending on their own values, demonstrating that the application of 'evidence' in evidence-based medicine is far from being a neutral, apolitical process.

Given the political and social processes at work, as well as the inherent uncertainty of the evidence itself, it is unsurprising that evidence-based recommendations can change significantly over time. This can be as a result of new (perhaps more 'valid') evidence becoming available,[12] however guidelines can also change simply as a result of existing evidence being reinterpreted.[13] The EBM

[12] One example of this is the results of a recent trial showing that babies given peanuts appear to be less likely to develop a peanut allergy, directly contradicting previous health advice that babies should not be fed peanuts because of an *increased* likelihood of developing an allergy (Du Toit et al., 2015).
[13] For instance, the recent NICE guidelines on caesarean section presented revised advice on the safety of the procedure without any new data being used, instead the new statistics were based on a

framework itself acknowledges the issue of uncertainty: the priority placed on systematic reviews and meta-analyses acknowledges that individual trials may give misleading or conflicting results, and the process of updating and revisiting both reviews and clinical guidelines is intended to account for new evidence becoming available and for 'improvements' in analytical methods. There is clearly, therefore, no one way to interpret evidence, and this ambiguity means that evidence-based decision making can never be a purely objective and neutral process. In this context, it is unsurprising that individual clinicians, and indeed patients themselves, might choose to overlook some or all of the official evidence. EBM proponents tend to view such behaviour negatively, for instance becoming frustrated with doctors failing to interpret RCTs 'properly' (Edwards, 2007), however Marks (1997) raises an important question: given the uncertainty inherent in all forms of evidence, at what point does disagreement over the results of an RCT become irrational behaviour? The EBM framework struggles to address this issue because the very basis of its credibility is its purported objectivity, i.e. its claim to remove politics and power relations from medical decision making by using neutral scientific evidence. As Marks puts it, EBM seems "incapable of addressing matters of science and politics in the same breath". Thus, despite acknowledging statistical uncertainty in specific trials, the EBM framework appears to be largely unwilling to engage with the greater uncertainty and subjectivity involved in interpreting the evidence base as a whole.

The fundamental and wide-ranging concerns discussed above, along with the mutability of trials I discussed in Chapter 4, have led many commentators to argue that the hierarchy of evidence advocated by EBM is too restrictive, and that a more nuanced understanding of evidence is warranted. Cartwright (2011) argues that the EBM evidence framework, with its reliance on RCTs, is essentially designed to find individual "clinchers", rather than seeking a body of vouching evidence. She suggests a more nuanced approach to evidence in medicine would seek to understand

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recalculation of previously available data. Based on these new risk estimates NICE concluded that planned caesareans are not significantly riskier that planned natural births, and that from a medical (as opposed to financial) perspective there is no reason not to allow women to choose either option (NICE, 2011). This conclusion overturned previous NICE guidelines, and also challenges a key health policy aim (endorsed by the WHO) of reducing the percentage of births that take place by caesarean.

"capacities" and underlying principles, rather than merely looking at whether a treatment works in one particular setting for an RCT. This view is echoed in Bluhm's argument that there is a need for more connection between the different levels of evidence, and in particular that the 'highest' evidence from RCTs must be understood in the context of the 'lowest' evidence from laboratory work and clinical experience, in order to better understand individual rather than group responses (Bluhm, 2005).

These calls for a more nuanced approach to evidence are reflected in Cambrosio et al.'s (2006) discussion of mechanistic versus regulatory objectivity. Mechanistic objectivity, which is a manifestation of the crude version of EBM discussed above, is embodied in a system that relies on checklists and guidelines. Regulatory objectivity, in contrast, "turns the focus away from objects towards collective forms of expertise combining people (clinicians, researchers, administrators, patients, etc.) and objects (entities, instruments, tools, techniques, etc.) connected by specific coordination regimens." Under this approach, which reflects the more nuanced approach to evidence presented in much of the academic EBM literature, the focus is moved away from the *outcome* of evidence interpretation to look instead at the *process* through which a consensus is reached. As well as providing a normative framework for a more nuanced approach to evidence, the concept of regulatory objectivity also provides a useful analytical framework for exploring the role of evidence in cell therapy innovation. By focussing on how evidence is conceptualised and used in decision making, we can better understand the complex and interdependent relationship between the different domains involved in clinical research. In the analysis which follows I use this framework to analyse empirical data from my fieldwork, examining how different actors in the field understand and mobilise the concept of evidence, and the affordances it provides them. Underpinning my analysis are two key themes from the epistemic critique of EBM, which I will return to at the end of the chapter. Firstly, I consider whether the crude version of EBM that is the subject of such criticism is in fact apparent in cell therapy trials, or whether the more sophisticated, nuanced version presented in the academic literature is also visible 'on the ground'. Secondly, I explore the concepts of mechanistic and regulatory objectivity, examining how regulatory institutions and cell

therapy developers interact to produce and evaluate evidence, shaping both the development of specific therapies and the very definition of evidence itself.

7.2 RCTs and cell therapies - the 'right' kind of evidence?

In line with the crude version of EBM described in the previous section, many interviewees described RCTs being treated as conclusive proof of the potential of a new therapy. For instance, Interviewee 7 described how two RCTs failing to show efficacy effectively halted any further research into a treatment:

> "The Americans then did some double-blind placebo-controlled trials where they took patients and either gave them a transplant or a pretend transplant and found that there was no significant benefit. And they published those papers at the beginning of this century, and the sort of perception in the world was that that was the definitive statement that these therapies didn't work." (INT7)

The negative effect of an unsuccessful RCT is highlighted by this quote from Interviewee 11, talking about a company completely abandoning the development of a cell therapy after unsuccessful Phase 3 studies:

> "They went from not real good open label Phase 1 type of studies, then they went immediately into Phase 3 studies … and there's positive signals going on, but they didn't hit their primaries and so they've gone in a different direction." (INT11)

Interestingly, it is not just unsuccessful late-phase trials that can hamper the development of a product; Interviewee 17 explained that he was concerned that even for his first-in-man trial, unpromising results would make it difficult to continue developing the product:

> ""From a commercial perspective, you know, [a disappointing trial result] sounds rubbish - and then how do we raise further funds on what some would regard as dubious data?" (INT17)

It seems, then, that evidence from any trial, regardless of phase, can have a significant impact on funding and regulatory decisions, meaning it can be problematic for cell therapy developers if a trial delivers the 'wrong' result.

Although these quotes demonstrate the importance of trial results, they also suggest a certain ambivalence towards the way the evidence has been or could be interpreted, and a recognition that decisions based on such evidence can be flawed. This raises the question of how trialists themselves conceptualise evidence, and in particular the extent to which they embrace or reject the evidentiary expectations of EBM. In this section I will explore trialists' perspectives on evidence, first by examining how my interviewees perceived the validity and utility of the evidence generated by trials, and then by looking at how cell therapy trials are challenged by dominant discourses of evidence, in particular by the focus on randomised control groups, and how they also challenge these discourses in their turn.

7.2.1 Trialists' perspectives on evidence

Most interviewees were in favour of structured, regulated clinical trials for experimental therapies, and rejected other forms of evidence (such as individual case reports) as less valid. For instance, Interviewee 5 explained that he had moved straight to a clinical trial rather than considering a Hospital Exemption (HE) licence for his treatment, mainly because he felt that the collection of evidence from 'proper' trials was important for the scientific development of the field:

> "It's not good science really, because what we really need, especially in cell therapy, are properly designed clinical trials to be executed and completed. And we still see even now in my field some really uber-eminent people publishing case reports and series, and two or three patients in the New England Journal of Medicine. And they are remarkable results, but that's not a proper clinical trial." (INT5)

In this quote, Interviewee 5 is clearly sceptical about the evidence generated by individual clinical cases, and feels that it should not be published in a high-quality journal. Interviewee 9 was also sceptical about evidence generated from individual

cases, although in his case his worry was that it would not be publishable at all, or would not be accepted as evidence for further clinical development:

> "We thought about specials licences and all sorts of other ways round it, but at the end of the day we knew we wanted to publish our data. And if we didn't go through the regulatory route we wouldn't be able to publish it, or we certainly wouldn't be able to use those data in terms of the next phase of our work … I think there was some nagging doubt that had we not gone through the regulatory process would it disqualify our publication from that journal." (INT9)

The fact that so many interviewees were in favour of structured trials thus appears to be motivated not only by the belief that they generate more robust evidence than clinical experience alone, but also by an awareness that trial evidence is more likely to be aligned with the expectations of key decision makers in the future.

Because of the general acceptance that evidence from individual cases in less valid than 'proper' trials, many interviewees felt that treating patients under HE was only appropriate if there was already evidence that the treatment worked, rather than HE itself being a way of generating that evidence. For instance, Interviewee 6 explained that she produced MSCs for trials when they were used in an experimental context, but for Graft vs. Host Disease they were produced under HE *"because it's already quite clear that they work".* This perception was also reflected in Interviewee 1's description of the discussions he had with the MHRA when considering how to approach a new cell treatment his centre wanted to start offering to patients:

> "There is good evidence that it works, so it wasn't that we were going to do it for the first time. So we did discuss, well is there any point in doing a trial of 20 patients - you could call it a feasibility study or whatever. But in reality we're not testing anything other than your own ability to do it, because it's been done in other places. And, well, their [the MHRA] advice was to do it under a specials licence, which is what we did." (INT1)

The contrast with a more experimental treatment is highlighted by his description of another treatment which had not yet been used extensively elsewhere:

> "When there was no evidence that they were effective - so it was effectively a first-in-man trial - well why would you give it apart from in a trial? I mean there's no point." (INT1)

The contrast between these perspectives on established versus more experimental treatments further emphasises the extent to which trialists accept the EBM hierarchy of evidence, whereby trials are the only means of generating valid evidence of the safety and efficacy of a new treatment.

In contrast to these views about the inferiority of the evidence generated from individual cases, some interviewees did recognise that there could be benefits to treating a small number of patients under HE. For instance, even though he had decided against this approach, Interviewee 5 acknowledged that there could be an argument that it could facilitate a future trial:

> "I have heard people say, you know, if you have one or two cases like that it helps you with regulators to get your trial approved." (INT5)

This view was also taken by Interviewee 13, who expected to need evidence from a number of compassionate-use cases (undertaken outside the UK) to support the case for a clinical trial:

> "We've only one patient successful, and unless we get two or three more in Poland I don't think there's any chance of us getting ethical approval here anyway." (INT13)

As well as supporting the case for ethical approval, treating patients under HE also provides an opportunity to refine the process and ensure the trial is successful: as Interviewee 4 said, *"it may inform how we do the trials".* Interviewee 17 also recognised this as a benefit, explaining that reducing the pressure to move into clinical trials too early would allow developers to ensure their product was ready:

> "You're not scrabbling to get to Phase 1 too quickly, and not take chances, but maybe not refine the product as well as you would like to." (INT17)

He went on to consider whether there was an argument for creating a more regulated HE framework that could to some extent replicate the conditions under which organ transplantation was developed, but reduce the associated risks:

> "All of that experimentation occurred because the clinician could do what they liked, there was no approvals required so they had a safe environment to do that work. And we're not too far removed from that, and yet we have the regulations that we have to comply with - which is fine, but there's a way to kind of learn from that. And maybe that's why the compassionate use or the specials licence, if it can be made maybe slightly more robust so that people don't take advantage, it's a good place to refine the technology in a safe environment." (INT17)

It seems, then, that there are two conflicting perspectives on the use of HE for experimental treatments: the 'inferiority' of the formal evidence generated means that it is only suitable for treatments that already have evidence of efficacy, but on the other hand it can generate useful information to facilitate future trials, potentially offering a 'safe space' for innovation.

From the trialists' perspective, it appears that the main drawback of compassionate use cases is the lack of a structured, consistent approach to the collection of data on outcomes. This is highly systematised and regulated in a clinical trial, whereas for individual cases there is much less oversight, as highlighted by this quote from Interviewee 4:

> "There is a database of patients, and it's a voluntary system. And to be honest it's not a very good database, but the principle is there." (INT4)

Such informal approaches to data collection can lead to inconsistent reporting, have significant potential for errors and omissions, and require a significant amount of work to collate, as highlighted in this quote from Interviewee 6:

> "Some centres are excellent at giving us back feedback on how the therapies are going, but even if it's just an email saying, you know, 'the diarrhoea was two and a half litres yesterday and now it's only down at two', you can begin to pull it all together." (INT6)

The use of data from individual cases also faces challenges associated with the characteristics of the patients treated, equivalent to the exclusion and inclusion criteria for a trial. For instance, Interviewee 4 explained that when looking at the outcomes for patients treated under HE, he had to take into account the reason they had not been in a trial instead, as this was likely to affect the outcome:

> "It depends why they're not in a trial - if they're not in a trial because there wasn't a trial then I suppose you hope that the data would be very similar whether they'd been in a trial or not. If the patients weren't in a trial because they weren't well enough to be in it then you might expect the results to be slightly worse than average." (INT4)

The main drawback to individual case reports, then, appears to be the lack of a standardised patient cohort and data collection process.

Interestingly, the way that trialists perceive the advantages of trial evidence is actually very similar to the benefits they see in individual cases, with the addition of a more standardised approach. For instance, Interviewee 17 was conducting a non-randomised study, which would build on the experience of compassionate-use cases by providing more standardised data:

> "Because the clinical trial will have hopefully a reasonably standardised group of patients, as standardised as we can because they're very heterogeneous anyway … it will be much a more consistent dataset. So the product for each patient will be the same - give or take what the patient needs specifically - but the product

> will be the same, so we'll hopefully generate a lot of information from that that will be additive to the compassionate use data." (INT17)

In this description, the trial is actually more like a series of case studies - a small number of patients with no randomised control group, but a structured and standardised protocol which make it possible to collate and extrapolate from results. This view of early-phase trials was held by a number of other interviewees, as shown in these quotes:

> "I always saw this as in one sense being a series of observations, because we can't do very large numbers and there were a lot of complex issues." (INT4)
>
> "What was done was four patients in Poland, which I wouldn't even call, I suppose it was registered as a clinical trial with the FDA, but I would call it highly experimental on a one-by-one basis." (INT13)

Early-phase trials, then, appear to have much in common with compassionate-use cases, and whilst the evidence generated is considered more 'reliable', this has more to do with standardisation of processes and data collection than randomisation or blinding.

7.2.2 What price randomisation?

These findings suggest that although cell therapy developers are largely in agreement that clinical evidence should be generated through regulated trials, they are not necessarily convinced that randomisation is essential. Indeed, a number of interviewees felt that even in a randomised trial, much of the useful evidence generated was not in itself randomised. For instance, Interviewee 4 explained that because his trial was a cross-over design it was possible to examine the effects of giving one treatment before or after another, even though this element of the trial wasn't randomised:

> "You then get a sequence effect as well, which is obviously not randomised, by definition obviously, but actually yields other information." (INT4)

The accumulation of temporal data was also referred to by Interviewee 17, who felt that this was an additional benefit of his trial:

> "It does serve as, not necessarily an experiment, but it's data that's cumulative that you can't generate any other way." (INT17)

In this quote, Interviewee 17 was careful to distance himself from any 'scientific' claims because of the lack of randomisation, whilst still recognising the benefits of such data, aligning with the previous quote which highlighted the additional, non-randomised data that was generated alongside more formal outcomes. Some interviewees went further than this, however, by questioning whether randomisation is always necessary at all; for instance, Interviewee 7 made the argument that in some circumstances a blinded control group is not necessary to prove a treatment works:

> "What I'll say to my American colleagues is that I don't need to do a double-blind placebo-controlled trial - if I have someone 15 years after a transplant who has a [measure of disease progression] which is less that when they presented 25 years previously, on no treatment, with a scan that shows [measure of disease] back to normal … it shows it works. I don't need any trial to tell me whether this therapy has an effect." (INT7)

Clearly, then, randomisation is not the only means of generating useful evidence for cell therapy trialists, and in some cases is not perceived to be necessary at all.

Unsurprisingly, these perspectives led some interviewees to question whether the primacy afforded to randomised trials by regulators and funders is justified. Some raised the issue that the design of a trial, or the way the data is analysed, can change the overall results. For instance, Interviewee 7 explained that the results of the two early trials in his area had been taken as a definitive answer on whether the treatment worked because the trials were 'proper' RCTs. However, he argued that if the sub-groups had been defined differently the trials would have shown different results, suggesting that the randomisation process did not have some intrinsic benefit that ensured the results was correct, despite being interpreted as such:

> "They took 11 patients and gave them surgery, took another 11 I think and gave them a small transplant, and 12 and gave them a big transplant, and then compared 11, 11 and 12 and found no significant effect. If they'd pooled the transplants …they would have had a significant effect." (INT7)

In this example, the lack of a significant effect is due to a power issue: because the sample was broken down into smaller groups, a larger effect size was required to generate a statistically significant result. In another example, raised by Interviewee 14, the unsuccessful results of a trial (in this case not a cell therapy trial) were a result of the treatment only working in a particular sub-group of patients:

> "They'd decided it had failed … it didn't work. And by stratifying patients with different types of asthma they were able to show that in one type of asthma it worked brilliantly, and in another type of asthma you'll see no response. So in a mixed cohort you'll never pick that out." (INT14)

There were also instances where the results themselves were not in question, but rather the interpretation of these results; for instance, Interviewee 17 queried what would count as 'success' for his therapy:

> "Our surgeon said, with sick patients if we can after a year still keep 50% of them alive - from his perspective that's a success. But somebody else looking at that, you'd think you're doing a clinical trial and half the patients die. If the first trial was with four patients … if we had two out of the four patients who passed the primary outcome and two that didn't is that regarded as a failure?" (INT17)

For cell therapy trialists, then, whether or not a trial generates valid evidence is contingent on much more than just the typical EBM markers of 'quality'.

We can see here two very different perspectives of evidence emerging: the EBM model, developed largely for pharmaceutical trials, which emphasises blinding, randomised control groups and large sample sizes, and the model required for cell therapies, where trialists do not necessarily view all these elements as necessary, and

in fact they may not even be possible. For instance, it will often not be practical to recruit the large numbers of patients generally seen in Phase 3 pharmaceutical trials, as explained by Interviewee 2:

> "A surgical trial, where you're tailoring the treatment to the patient, different numbers of cells in different placements, immediately it's anathema to a trial design specialist. You're always going to be doing it in cases of 30 or 40 patients … not 600 for power calculations." (INT2)

Sample size was also a problem for Interviewee 7, who described his experience discussing trial design with statisticians who were unfamiliar with the realities of cell therapies:

> "They'll say, you know, you need 80 patients, you need to randomise to this arm and this arm and you need to do this. And you say, well I just can't do that. I just simply cannot do that." (INT7)

Another problem Interviewee 7 highlighted is the difficulty of blinding surgical trials, which I discussed briefly in Chapter 3. He explained that he was unwilling to have a blinded control arm in his trial because the treatment required an extremely invasive procedure for implanting the cells. Blinding would mean some patients would be put through this invasive procedure only to receive a placebo, which he considered to be unethical. He explained that although this approach was accepted by regulators, it was challenged by other clinicians in his field:

> "Most of the people who dominate the world of [clinical area], especially the world of [disease], are people who've cut their teeth in pharmacological trials, so the idea that you don't do a double-blind placebo controlled trial is completely [alien to them]." (INT7)

This experience highlights how key components of trial design can be contested, and what might be considered essential by one trialist might be expendable to another, as Interviewee 7 went on to emphasise:

> "They'll say to me it's unethical to not do a control arm … so I always say well I think it's unethical that you haven't followed your

> patients up … I wouldn't need to do this trial if you'd done your job properly." (INT7)

Here we can see the extent to which the pharmaceutical trial model, with its emphasis on randomised, blinded control groups, has become the default expectation in some clinical circles, and the difficulties this can cause for a treatment that does not fit into this model.

The conflict between different perspectives of validity also extends to the analysis of trial data, for instance Interviewee 7 explained that he wanted to review the results of previous trials to understand why the treatment had not been effective:

> "One of the things I always say, for example, is why don't we go back and look at the data on cell-based therapies and see who's done well - so what is it about the people who've done well vs. the people who've done badly. And they say well you can't do that … you're cherry picking." (INT7)

What he saw as essential analysis which would help him find ways to improve the treatment was met with accusations of data dredging by colleagues primed by the EBM literature to be suspicious of any attempt to reinterpret trial results to find a more positive outcome. He then went on to draw a clear distinction between his work as an academic researcher and the behaviour of pharmaceutical companies:

> "People have this huge suspicion of all of this, and you say well there's nothing wrong with it I'm not trying to sell a product." (INT7)

It seems, then, that cell therapy trialists may struggle to have their version of evidence accepted by a clinical community that has been trained to be suspicious of corporations attempting to 'spin' the evidence for profit, even when there is no commercial motive involved.

There are clearly tensions between the version of evidence promoted by EBM and that of cell therapy trialists, and my interviews suggested that these tensions also extend to the scientific research underpinning these trials. This is exemplified by the fact that the scientific data being collected in the trials I reviewed often did not have

a clear purpose; for instance, when I asked Interviewee 4 what why biopsies were being taken during the trial, he replied:

> "It's we've got patients who are being treated, let's at least collect samples and see what we're going to do with them." (INT4)

Scientific outcomes for trials, then, do not always have a specific objective at the outset, unlike the clinical outcomes which (in theory at least) have to be completely specified before the trial starts. The tension between these two approaches was highlighted by Interviewee 8 (a trials specialist):

> "The basic scientist's approach to analysis is very different to a trialist's approach. If you're running clinical trials everything has to be pre-specified, spelled out, you have very clear analysis plans that we agree up front. Basic scientists don't tend to work in that way, they do much more exploratory type analyses, or fishing expeditions as some of us may refer to them." (INT8)

There is also a marked difference between the scientific and EBM approaches to evidence when it comes to publishing: trials are expected to publish both positive and negative results, to address the issue of publication bias, whereas in science there is still a tendency to publish only statistically significant results. Again Interviewee 8 explained this difference from the EBM perspective:

> "The difficulty comes - and this isn't a criticism of the basic scientists - but they'll publish it if they get the p-value they want, but they don't if they don't get the p-value that they like. Whereas if we have discussions about it, well yes you can have those data to do those analyses on the understanding that you write them up whatever they show." (INT8)

It seems, then, that the clinical trials framework prescribes a rigid, prospectively-defined approach, whereas the biological research process, although it adheres to (and in fact inspired) the experimental model advocated by EBM, tends to have a less formalised approach to hypothesis testing and the reporting of results.

Overall, these findings suggest that cell therapy trialists are generally positive towards the concept of regulated trailing, and view the evidence generated as more reliable than other forms of clinical evidence. However, the benefits they perceive largely stem from the more structured, standardised approach of a trial, rather than randomisation, blinding and statistical power, which are at the heart of EBM's conceptualisation of evidence. Furthermore, much of the evidence valued by cell therapy trialists is generated without the need for some or all of these features, suggesting that although researchers can learn a lot from trialing a therapy, not all of this relates to the formal outcome measures of the trial. Webster and Faulkner (2015) argue that the trial process produces outcomes that are often far removed from the original protocol, and this is certainly the case here, with trials being used to progress the science, refine the treatment and understand the logistics of delivery, alongside more traditional tests for safety and efficacy. Clearly for cell therapy trialists there can be multiple outcomes of interest from a trial, and multiple ways in which an outcome can be significant. The gap between this perspective and that of EBM reflects what Keating and Cambrosio (2012) describe as the 'cognitive dissonance' between statisticians and clinicians, something that was very apparent in my own research. This dissonance, however, does not appear to be universal: my findings suggest that many clinicians have in fact embraced the dogma of EBM, applying the crude version that insists on certain aspects of trial design being essential for evidence to be considered valid. This self-policing amongst the clinical community may prove problematic for the future adoption of cell therapies, where these key tenets of EBM are often logistically impossible.

The fact that many clinicians appear to accept, and enforce, the version of evidence set out by EBM is perhaps unsurprising, given the extent to which it has dominated clinical research for the past two decades. The fact that cell therapy trialists, who are of course also clinicians, often reject or question key aspects of the EBM model means that they are swimming against a strong tide, which increasingly includes not just statisticians and the trials community but also members of their own discipline. This disconnect is partly caused by the practical problems associated with cell therapy trials, which mean, in the words of Interviewee 7, that cell therapy

developers *"have to be a bit imaginative in how we do the trials".* Another contributory factor may be the close links between clinical cell therapy research and basic science, which as we saw in the previous chapter are intertwined and interdependent aspects of the translational process. Marincola (2003) argues that the scientific culture can be problematic for translational research: for instance, the need to generate positive results for publication in prestige journals can make scientists unwilling to embrace the uncertainty of clinical research, instead encouraging them to 'drop the ball' early in the translational process if results are unpromising. My findings suggest that this scientific culture, and in particular the way that it approaches evidence, is significantly detached from the dominant discourses of EBM, a tendency that is also apparent in the philosophy of science critiques of EBM which I discussed earlier in this chapter. Thus, cell therapy trials take place in a context where alternative conceptualisations of evidence are both necessary and accessible, making it unsurprising that cell therapy trialists do not wholly embrace EBM rhetoric.

Clearly, then, there are significant tensions between the concept of evidence set out by EBM and that which is enacted through clinical and scientific research. There is no denying, however, the powerful effect of EBM's rhetoric, as the effect of unsuccessful trials reported by my interviewees demonstrates. Moreira (2005) describes competing regimes of hope and truth in medical innovation, and for cell therapies trial evidence is clearly being interpreted as the 'truth' that holds the 'hope' represented by media hype to account. The nuanced version of evidence apparent in the clinic and the lab, however, suggests that there are many ways to interpret trial results, and indeed my interviewees felt that in some cases adherence to EBM dogma led to an invalid interpretation. On the face of it, this readiness to abandon treatments on the basis of evidence from one or two unsuccessful trials lends further support to Daley's (2012) argument against rushing into clinical trials. My interviews suggest, however, that other approaches could also help to reconcile the tensions between EBM and cell therapy translation, including a more structured HE framework that would provide a 'safe' space for clinical development as a precursor to formal trials, and a more nuanced approach to interpreting trial results that takes into

account the complexity of the treatments, and acknowledges the significant impact that trial design can have on the eventual results.

7.3 Trial endpoints: measuring progress, creating meaning

One of the most important factors in the design of a trial is the choice of endpoints, and in particular how the primary endpoint is defined. The term endpoint, as I use it here, combines two interlinked concepts: the outcome measure and the expected difference in this measure between the different arms of the trial. Outcome measures, as defined in EBM, are the specific metrics that the trial will assess, and are usually broken down into three categories: 1) primary outcome (or outcomes), which is the outcome the investigator thinks is of greatest significance, and should be defined at the time the study is designed; 2) secondary outcomes, which are other measures of safety and efficacy used to evaluate additional effects of the intervention; and 3) exploratory (or explanatory) outcomes, which are other measures, not associated with safety or efficacy, which could help to explain the results or aid in the design of future trials (CONSORT, 2017). Trials are supposed to be adequately 'powered', which means that the sample size should be large enough that the expected effect of the treatment, if observed, would be statistically significant. Significance, in a statistical sense, relates to whether any difference in outcomes between trial arms is most likely to be due to chance or to the effect of the intervention. This is influenced by two factors: effect size (the size of the difference in outcomes between the trial arms) and sample size (the number of patients in each arm). This precise definition of outcomes and significance, both prospectively determined and 'objectively' applied, is central to the version of evidence at the heart of EBM. During my fieldwork, however, I encountered a number of approaches to outcomes and significance that diverged from this, suggesting that in fact they are both highly mutable concepts, and the ways that cell therapy trialists mobilise these concepts can materially affect the 'evidence' generated by a trial.

7.3.1 Choosing outcomes - the art of the measurable

Many of my interviewees were concerned that the outcome measures used in their trials were not good representations of the actual experience of the patient. In some

cases, this was because the 'objective' outcome measure being used did not align with the patient's subjective experience, as in this example from Interviewee 17:

> "And then the patient might give you a really high quality of life reading, but actually when you measure them clinically they're not, it hasn't made that much different. But they think it's been great, because they're in such a poor state to start with." (INT17)

In a similar example, Interviewee 9 described a trial where the outcome measure didn't appear to show improvement during the trial, but over a longer period the patients themselves reported a change in their experience of their disease:

> "There'd be patients in whom we'd say 'well this treatment's not worked' and we'd abandon the study. And a year later the patient would say 'well actually I think my disease is different from how it used to be'. So I think it did achieve something, but you just didn't recognise it – the patients haven't said that but that's what we think. But it's hard to put into words, we don't have very good measurements." (INT9)

This quote highlights the difficulty of defining and measuring improvement, particularly in cases where there is no gold standard prognostic tool, as was the case for Interviewee 7:

> "And everyone knows that's not the most sensitive way to measure things. So it's an inadequate tool, but it's probably the best tool we have - or at least it's one of the best tools. So the problem is everyone agrees that it's not the best way to measure it, but we measure it anyway. And once everyone's done it enough times you can't use anything else." (INT7)

This quote also highlights another issue with outcome measures, which we first encountered in the discussion of temporality in Chapter 5; it is often necessary to use the same outcome measures as previous trials in order to compare the results, even if these are not considered the best measurement by the trialists themselves, or indeed the wider clinical community.

Agreeing on the most appropriate way to measure progress is challenging for any trial to some extent, but, for some of my interviewees at least, cell therapy trials have specific characteristics that make it particularly problematic. For Interviewee 1, the main difficulty was that because cell therapies are both expensive and risky, he felt that it was important to ensure they were measuring something that was really relevant to the patient:

> "I suppose the issue is that cell therapy is quite expensive, and it's now quite toxic as well. So progression-free survival, it doesn't mean anything to a patient, whereas being cured does mean something - it's quite clear." (INT1)

However, other interviewees felt that patient-relevant outcomes were actually less important for cell therapies; for instance, Interviewee 15 argued that it is necessary to understand exactly what is happening clinically in order to be sure the treatment has worked as hoped:

> "The problem might be if you send it to an orthopaedic trials unit at this point it would just be about patient-reported outcome measures or something. Which would be OK, but we're not entirely getting to some of the aspects of a regenerative therapy, which might be to some extent based on a tissue response. So that's an aspect that needs to be brought into it." (INT15)

The difficulties of measuring progress, and the conflicting priorities of patient relevance on the one hand and 'measurable' clinical difference on the other, led some interviewees to endorse using a number of different measures in conjunction:

> "The only feasible approach is to have a really broad, comprehensive clinical assessment of progress, and multiple measures of progression." (INT2)
>
> "We're trying to collect lots of measures … I would love to move away [from] these primary endpoints, and to have a bit more of a sort of vector of change, or a sort of summation of change." (INT7)

It seems, then, that focusing on a singular primary outcome, as EBM best practice demands, is not viewed by many trialists as a valid way to assess the clinical outcome of a cell therapy.

Another factor that my interviews suggested could be problematic, or at least worthy of consideration, is the appropriate length of outcome measures for cell therapy trials. Views on this differed markedly between clinical areas, for instance in cancer there are well-established, accepted outcome measures that tend to be relatively short-term, meaning a trial can typically be conducted, analysed and reported in one or two years. For other conditions, however, the length of time required to measure outcomes may be much longer; this is particularly the case for more regenerative therapies which involve cell transplantation, as highlighted by Interviewee 7:

> "When you implant cells they obviously have to survive, they have to grow, they have to mature … the best results of a transplant take three to five years before you see an effect. So if you look at six months or a year … you might not see the optimal response." (INT7)

Longer outcome measures are problematic because inevitably the overall research process takes longer, contributing to the problems with trial temporality that I discussed in Chapter 5. Another issue with long outcome measures is that they make it more difficult to use adaptive trial designs, which involve making changes to the trial as data is accumulated, as Interviewee 15 explained:

> "It kind of depends how quickly you can understand the effect of your treatment though doesn't it … so I think in cancer, presumably - I'm not a cancer scientist - but presumably the imaging would tell you and the markers would tell you about response reasonably quickly. In our field I'm not sure we have those biomarkers yet, and I'm not sure we have those imaging modalities yet that would allow you to respond as quickly." (INT15)

The speed with which an outcome can be measured thus represents a point of difference between different therapies, with significant implications for both the practicality of trials and the way that evidence of efficacy might be interpreted.

The difficulty of choosing appropriate outcome measures is compounded by the importance of the decision: the success or failure of the treatment is essentially defined by the primary outcome measure. The implications of different choices can thus be the difference between a treatment being deemed to work or not, as highlighted by this quote from Interviewee 7 about an unsuccessful trial in his area:

> "If they'd taken the [outcome measure] and done it at two years, instead of asking people if they were better at one year, they would have got a significant effect." (INT7)

Unsurprisingly, then, many interviewees reported taking great care when specifying the primary outcome for the trial, thinking carefully about which measures were most likely to show success. For instance, Interviewee 17 explained that his team decided against using efficacy as the primary outcome for an early phase trial to avoid the risk of missing the endpoint and having the treatment deemed a failure before they had had time to develop and refine it properly:

> "Phase 1 was initially going to be a transitional Phase 1/Phase 2 trial, but we realised that there are too many uncertainties in the outcomes because we haven't been there yet - that actually putting performance outcomes as primary outcomes, efficacy outcomes as primary outcomes is a dangerous thing to do in a first trial. So we've backtracked from that and put safety outcomes as the primary outcomes, because then it becomes more arbitrary about what's good and what's bad." (INT17)

Here we can see trialists working with the fluid nature of the evidence generated by clinical trials, essentially working within the framework to give their trials what they perceive to be the best chance of success. We can also see that despite the rigid nature of the primary outcome, what counts as success is actually a very subjective

issue, with implications for both the measurement of efficacy and the design and feasibility of the trial.

7.3.2 Expected effects - the definition of success

Alongside the choice of primary outcome measure, another factor that can affect the perceived success of a trial is the effect size it is designed to measure. The choice of effect size is crucial, because this is what will be used to determine whether the treatment works, and my interviewees often reported difficulties in deciding what the effect size should be. Sometimes this was because the treatment was so unique that patients had no other treatment options, meaning there was no data to use as a comparator, as was the case with Interviewee 17:

> "And it's fairly arbitrary, because you're not comparing to something that exists." (INT17)

In a similar example, Interviewee 7 was trialling a cell therapy in a group of patients who would not usually be treated for the disease in question, and again this meant there was no comparative data available:

> "This is being used now in a group of patients who have never been used in [disease] because they're earlier stage. So, you know, you have to have all these power analyses … based on the size of effect you want to see, and we don't quite know what the size of effect is going to be." (INT7)

In other cases, the outcome measure itself was unfamiliar, again making it difficult to predict what sort of effect might be achieved, as highlighted by Interviewee 8's response when I asked if using imaging as a primary outcome presented any difficulties:

> "It's only more challenging if it's a primary outcome that you haven't used before, so therefore you're less certain as to the properties of the data that you're going to get, what the data are going to look like. And that's got nothing to do with it being a cell therapy, that would be equally applicable to any choice of outcome

> that was an outcome that you hadn't got the experience of working with previously." (INT8)

Unfamiliar, or uncertain, outcomes are also another barrier to the use of adaptive designs, for instance Interviewee 17 explained that one of the reasons they decided against an adaptive design was that they didn't have the background data required to plan the prospective adaptations.

To counter the uncertainty caused by unfamiliar outcomes measures, some interviewees described working backwards from what would be considered clinically meaningful in order to decide on an appropriate effect size, as explained by Interviewee 8:

> "In terms of effect size, what we find for a lot of the what I would call early translational type work is that we work in hypothesised effect sizes … because we often don't have data on expected standard deviations or mean differences that we can base a sample size on. So it's based on an effect size which would represent, we think, something that would be relatively meaningful." (INT8)

This approach appeared to be not only a means of agreeing a target effect size for the power calculations on a particular trial, but also helped trialists to articulate what the treatment needed to achieve in order to be worthwhile. For instance, Interviewee 7 explained that his approach was based on working out how much better than existing treatments a cell therapy would need to be in order to be worth pursuing, essentially meaning that missing the primary endpoint would convince him, as well as others, that the treatment had failed:

> "If you're arguing that your therapy is marginally better than a placebo effect, then it's a therapy not worth having." (INT7)

Interestingly, this approach took the conversation away from statistical models and brought it back into the realm of the clinic, with a focus on the meaning for patients. For instance, Interviewee 17 described discussing the target effect size in detail with clinicians in order to ensure it would represent a 'good' outcome for patients:

> "With the clinicians we set a target of what would be clinically acceptable - what is a good clinical outcome - and then worked back from there where we can. With literature data on what that means for the patient group, how many patients would you need to get roughly to prove that." (INT17)

It seems, then, that trialists can to some extent address the rather abstract concept of statistical significance by focussing on the more tangible issue of clinical significance, although of course this too is a subjective, potentially contentious judgement rather than an objective fact.

When considering what would be a clinically meaningful effect size, one very important factor is the extent to which the effect is binary (i.e. it is either present or not present) or more incremental (i.e. a relatively small movement along a scale). Most pharmaceutical trials are designed (and powered) to measure incremental effects, and this is also the case for many cell therapy trials, particularly those testing non-regenerative treatments. For treatments where there is an expectation of cell engraftment, however, a more binary effect is often expected, with the treatment either succeeding or failing in a manner more akin to an organ transplantation than a drug. This has significant implications for trial design, and in particular for the sample size required, as highlighted by Interviewee 12:

> "I was talking to a pharmaceutical company, they've just done a Phase 3 trial trying to prove superiority of their ACE inhibitor over the competitor so that they could get into the ACE inhibitor market. It took six years, it involved 13,000 patients, and it showed no benefit - now you tell me how much that cost, to write off a drug at that stage. And then … they were talking to us about one of our therapies, and they said … 'how many patients are you [treating]?' And I said, 'well the statisticians have come back and said that 64 patients treated and 32 controls will tell you." (INT12)

Binary effects also create complications in terms of assessing the success of the treatment, essentially setting a different bar for what the target effect size should be. For instance, for a drug which has only incremental benefits a 50% failure rate might

be considered an ineffective treatment, whereas as Interviewee 17 explained the same failure rate for a 'curative' treatment might be considered successful:

> "Now there's no dose escalation there, you're not looking at safety of the product any more than you are looking at efficacy - it's going to work or it's not. And at the end of ten patients, five of them might be [cured] and five of them won't, but given the fact that 0% would have been [cured] without the operation that's going to be enough for people to want to do it." (INT17)

The difficulty of assessing what should be considered success is compounded by the implications of overpromising the curative potential of a treatment, potentially creating expectations that can't be met. For instance, Interviewee 7 explained how expectations surrounding his treatment could affect how patients would report their subjective experience of improvement:

> "If you go into a trial thinking you're going to have a cure, and you don't have a cure, you're going to … say I don't feel any different." (INT7)

In this context, the effect size used for the primary outcome measure on a trial can be crucial, as it sets expectations for what the treatment should be able to achieve. Interviewee 4 described how by setting an endpoint that involved an almost total cure he had essentially set his trial up to fail:

> "Something that has come back to haunt me a bit … we set up a primary endpoint that was very very exacting, and actually I would now set it up as a secondary endpoint. Because referees and statisticians are so rigid that they can't quite see that this was a primary endpoint that said that this is a life-changing therapy." (INT4)

Such unrealistic expectations of a cure can have significant consequences not only for the perceived success of individual trials, but also for whole fields of research, as highlighted by Interviewee 16:

> "My main qualm is that we will end up with what happened with the Clinton administration: a huge amount of money for Parkinson's disease with stem cells in the brain, and then it all went flop, and then for 20 years no one would invest in that … And actually when you look at the data it didn't go flop, it's just that people expected a miracle." (INT16)

These experiences suggest that the effect size a trial sets out to test affects more than just the success or failure of that particular trial, it also has a role in setting expectations for the treatment more broadly.

More than anything, these findings emphasise the extent to which trial protocols are shaped by various decisions about the outcomes to be measured and the desired effect of the treatment. This aligns with sociological critiques which have highlighted the contingency of this supposedly objective experimental method; for instance, Keating and Cambrosio (Keating and Cambrosio, 2012) contend that "as experiments, clinical trials require more than the mechanical application of routine methodologies; they require the definition of 'appropriate' research questions". My findings suggest that this is certainly the case for cell therapy trials, where the decision of what to test and how to measure it is clearly not an objective or neutral one. Choosing a primary endpoint involves a number of different and interlinked factors, including the outcome measure to be used, the likely effect size and the sample needed to reach statistical significance. Other factors also come into play when choosing endpoints, including how well it measures the actual benefit experienced by the patient, the length of time it will take to generate usable results, and the familiarity of the measures being used. There may also be difficulties caused by a lack of good measures of progress, and potential conflicts between 'objective' clinical measures and patient-reported outcomes, which are more indicative of whether the patient themselves feels their condition has improved, but potentially more likely to be affected by the patient's expectations. It seems, then, there are a multitude of ways that efficacy or safety can be defined, as well as various interpretations of what effect on these measures would be significant, and different

stakeholders might have very different views on which of these are the most useful or 'valid'.

Unsurprisingly, given the multiplicity of measurements available, the primary endpoint for any given trial is not inevitable, but results from trialists balancing a number of considerations, including what they feel would be the most clinically meaningful measure, what is most likely to be accepted by other stakeholders, and the ability to compare the findings with other research. My findings also suggest that an important consideration for many trialists is whether the endpoint is likely to be achievable, and/or the likely impact if it is not achieved. This suggests that the contingency involved in choosing endpoints is mobilised by trialists as a way to control the evidence generated by the trial, limiting the potential for 'bad' evidence, and maximising the chance of 'good', and it also highlights the significant role of trial endpoints in setting or reinforcing the expectations of a treatment. For instance, if the primary endpoint represents a complete cure then this becomes the bar the treatment is expected to meet, and failure to meet the endpoint means it has failed to live up to those expectations; conversely, if the endpoint is set at a lower level, then exactly the same results might be deemed a success. Likewise, by setting a primary endpoint that only evaluates safety trialists can avoid setting unrealistic expectations for a treatment early on its development, giving them more time to test and refine it before it is put to the test. The choice of endpoint can also in itself affect the evidence, by setting expectations amongst clinicians and patients which can then affect their perceptions of the outcome.

7.4 Regulation and evidence: seeking certainty in an uncertain world

The various ways that trialists themselves understand and mobilise evidence is clearly an important aspect of cell therapy trials, but it must also be considered in the context of the wider framework in which these trials take place. Most importantly, the way that regulatory and policy-making institutions approach the concept and interpretation of evidence is a significant factor in the translational process. Broadly speaking, these institutions use evidence for two purposes. Firstly, evidence is used

to regulate trials themselves, for instance when deciding how to classify a particular therapy, how a trial should be designed and undertaken, and whether it should receive ethical approval. These decisions tend to involve the Medicines and Healthcare Product Regulatory Authority (MHRA), with the Human Tissue Authority (HTA) also being involved in some cases. The Health Research Authority (HRA), Research Ethics Committees (RECs) and individual NHS trust R&D departments are also involved in assessing evidence and making decisions about the approval and conduct of trials. Secondly, the evidence generated by trials (along with other forms of evidence) is used to evaluate the safety, efficacy and/or cost effectiveness of a cell therapy, for instance in decisions about commissioning and reimbursement, or when an application is made for marketing authorisation. The European Medicines Agency (EMA) is responsible for assessing marketing authorisation applications, and reimbursement decisions could involve the National Institute for Clinical Effectiveness (NICE), NHS England (or Scotland), Clinical Commissioning Groups (CCGs) and individual trust commissioning processes. The different ways that these institutions approach evidence has a significant impact on trials of cell therapies, and on their eventual adoption into clinical practice. This section will explore institutional approaches to evidence by examining four of the key bodies involved - the MHRA, the HTA, NICE and the EMA - and will then go on to consider how these approaches can both enable and impede innovation.

7.4.1 Regulatory perspectives on evidence

The MHRA is the competent authority responsible for regulating and inspecting clinical trials for cell therapies designated as ATMPs, and is therefore the regulatory body which has most input into the trials process. Interviewees who had had dealings with the MHRA generally reported their relationship with the regulator being a positive one, as in this typical example from Interviewee 9:

> "I think on the whole the message from the MHRA is generally facilitative." (INT9)

Interviewee 9 went on to explain that this positive experience with the MHRA had not necessarily been expected:

> "It's funny, I remember it was a month of anxiety, and you're not quite sure what they're thinking and sometimes they come over as quite tough, and other times they come over as quite amenable. And in the end I went down there and talked to a few people and it was fine really - it was just a case of the two groups meeting." (INT9)

Interviewee 6 also had a more positive experience with the MHRA than expected, concluding that:

> "Do you know I think the MHRA are actually much less ogreous than you'd imagine them to be - they will talk to you, they'll talk you through it." (INT6)

Both of these quotes allude to the regulator's willingness to engage in a dialogue with trialists, which allows them to understand and address the specific characteristics of an individual trial, rather than rigidly adhering to a mechanistic approach. For instance, Interviewee 5 explained that for him the most important thing was that the MHRA took decisions based on a careful consideration of the actual risk involved:

> "You need to have someone that knows what they're doing and has a brain and can actually think about the issue, rather than take the tick box approach." (INT5)

It seems, then, that despite some initial nervousness that is most likely caused by unfamiliarity, trialists who engage with the MHRA tend to find the process constructive.

The MHRA's facilitative approach appears to result in, or even emanate from, a close relationship between trialists and the regulator, and it was notable the extent to which interviewees referred to specific personnel who they dealt with, such as in this example from Interviewee 5:

> "The person I mainly dealt with … she was absolutely fantastic. Not only was she, you know, not kind of hindering us as it were - as you kind of intuitively expect is going to be their role starting out - but she would actively advise, you know. And this is the way it should

> be actually, because the MHRA should be in the business of fostering these kinds of trials." (INT5)

These personal relationships appear to facilitate the negotiations needed to keep a trial running smoothly, as in this example from Interviewee 9:

> "Funnily enough we had a sort of a friend in the MHRA - unfortunately she's retired since we started doing this. And when I spoke to her what she said is, what you should do is rather than put it in as a whole new application, just put it in as an amendment, which we're doing." (INT9)

For some interviewees, these personal relationships extended to a close relationship with the institution as a whole:

> "Because of the new nature of this, and the academic basis of it, those of us who are developers in this field spend a lot of the time in discussions with the MHRA ... I've joked with [MHRA representative] the other day, he said 'we really should get you your own pass', I'm at the MHRA so often." (INT12)

Interestingly, Interviewee 12 (an academic researcher) went on to make a distinction between his own close relationship with the regulator and the more arm's length relationship that the private sector appears to cultivate:

> "On two occasions now I've written on behalf of the MHRA because they've been criticised by industry. And if you speak to anyone at the MHRA they will say it's very rare for industry to come and ask us our opinion or for our help, whereas academia are always coming." (INT12)

The importance of the MHRA's collaborative, flexible approach is emphasised by a comparison with the more rigid and less consultative approaches reportedly adopted by other institutions. One interviewee had significant problems with some of the requirements imposed by the HTA, which is responsible for regulating any cell therapy involving the transplant of human tissue (i.e. allogeneic therapies). These problems were largely caused by the requirement to conduct a blood test on the

donor at the time of donation, even though in this particular situation the results of the blood test would be invalid, and in any case a previous blood test taken the week before would provide all the required safety data:

> "They've ruled that if the law says you have to do an additional blood test you do it - you don't have to use the data. So think for yourself, in terms of the welfare of [the donor] at a stressful time - you take the bloods that we use, they come back for their procedure a week later, we have to collect additional needle sticks that's then not used for compliance. And it seems to me that that is explicitly unethical." (INT2)

He went on to conclude that the HTA was hampered by a 'tick box' approach to regulation, which he felt did nothing to actually improve the safety of the trial or the validity of the evidence generated:

> "They are dominated by compliance, by a paper trail … And all the infractions have been failures in paperwork, not failures in procedure." (INT2)

This inflexibility stands in stark contrast to the descriptions earlier of the nuanced, risk-based attitude that the MHRA appears to have adopted.

The inflexible and non-collaborative approach apparently adopted by the HTA was also experienced by some of my interviewees in their interaction with NICE, which is the body responsible for producing commissioning guidelines for cell therapies delivered by the NHS. For most trialists, NICE is not involved in terms of reimbursement for the actual trial: for publicly-funded trials the funding for the treatment is generally negotiated with individual trusts and clinical commissioning groups (although this in itself can be extremely problematic, as I discussed in Chapter 5), and for commercial trials the company funds the cost of treatment. However, for many trialists, particularly those developing treatments commercially, NICE must still be considered during the trailing process, because the trial needs to generate the 'right' evidence for reimbursement at a later stage. Interviewee 17 described the process of trying to ascertain what evidence NICE would require as extremely

opaque. He felt that this put the responsibility onto developers to decide what evidence they needed to submit, with the risk that NICE would then reject data that did not fit their expectations:

> "I don't think NICE are up to the job. I was at a conference that NICE put on before Christmas about data requirements for their reimbursement pathways, and pretty much they said that they rarely see a data package from a manufacturer … and they maybe have been approved by the MHRA to get marketing approval for the product, but pretty much every single one they dismissed as being substandard from a reimbursement perspective. And you just think, well what is it you need? And they wouldn't say what they needed, all they would say was we would tell you if you're in the right area, but we wouldn't tell you what it is." (INT17)

Again, this approach contrasts with the MHRA, which appears to be much more willing to engage with trialists in the early stages, discussing the types of evidence that will be required and advising on the best way to generate this evidence.

The importance of understanding how NICE is likely to interpret evidence is highlighted by the recent review of the guidelines on autologous chondrocyte implantation (ACI). Having reviewed evidence about both efficacy and cost, NICE released draft revised guidelines stating that ACI should continue to be funded only if used as part of a clinical study, because the evidence of ACI outcomes being better than microfracture (an alternative, cheaper treatment) was deemed to be inconclusive (NICE, 2015). NICE deemed the evidence of ACI's effectiveness to be "low quality", because of (amongst other things) small samples, inadequate follow-up, and lack of blinding. This is in effect a decision based on economic grounds, as NICE deemed that there was insufficient evidence to justify the additional cost of ACI, but I witnessed it having implications that extended beyond this. For instance, a trialist involved in designing a trial comparing ACI with a newer type of cell therapy explained that he felt the ACI-only arm was an appropriate control group, because the NICE assessment does not suggest ACI is *less* effective than the alternative, only that it has not been proven to be *more* effective. However, he described being challenged during

peer review for not having a 'proper' control group, because the peer reviewers, on the basis of the NICE assessment, viewed ACI itself as an experimental treatment (Field notes 23/09/15). Thus, although the NICE assessment was largely made on the basis of *economic* effectiveness - a combination of efficacy and cost - it was being interpreted as an indication of *clinical* effectiveness, and this then affected perceptions of the value of evidence generated by a particular trial.

One of the most interesting issues raised by the NICE consultation on ACI is the fact that two of the three products being assessed (MACI and ChondroCelect) have received marketing authorisation from the EMA, based on the same evidence as that assessed by NICE. To some extent this reflects the different remits of the two institutions, with the EMA being responsible for assessing whether a treatment is acceptably safe and effective, whereas NICE is also concerned with whether it represents value for money. It also, however, highlights the fact that different institutions may have different interpretations of evidence 'quality': for instance, in its approval of MACI, EMA refers to a study of 144 patients and deems this to have demonstrated its superiority to microfracture (EMA, 2013), which contrasts with NICE's evaluation that the study was too small to be reliable, and had an insufficient follow-up period. This apparent variability in assessing evidence quality is also apparent in other EMA decisions: for instance, the approval of Holoclar was based on retrospective, non-randomised data, albeit with a caveat that the approval is conditional on further data being submitted (EMA, 2015b). Interestingly, although it is specified that the further data required must be from a prospective clinical study, the decision does not explicitly state that such a study must be randomised (which may be due to the lack of an appropriate comparator and/or to the difficulties of blinding such a study).

The Holoclar example suggests that the EMA can be flexible about some of the key tenets of EBM, such as randomisation and prospective data collection. There are other cases, however, where it appears to have been less flexible, and perhaps even inconsistent, in its assessment of evidence quality. For instance, the rejection of Heperesc's MA application cited "concerns about the design and conduct of the studies, which cast doubt on their results and whether they could have occurred by

chance" (EMA, 2015c). In this case the evidence submitted appears to have been collected prospectively with the results compared to historical controls, which in theory should be deemed to be better quality than the entirely retrospective, uncontrolled data submitted for Holoclar. The other main difference was that the Heperesc evidence was based on only 20 patients, in comparison to 104 for Holoclar, which suggests the EMA may place more importance on sample size than on other aspects of trial design when assessing the quality of evidence. In contrast, however, the approval of Glybera was based on an uncontrolled study of just 27 patients, a decision that the EMA justified on the basis that "this is a subgroup of severely affected patients with a high unmet medical need" and on the "extreme rarity of the disease" (EMA, 2015a). Like Holoclar, the authorisation is conditional on further data being provided about the treatment as it is used, but there is no clear explanation as to why this is considered acceptable in these cases and not for Heperesc, which also aims to treat an unmet clinical need for a rare condition.

Many of my interviewees did not appear to be aware of or concerned by the EMA's approach to evidence, which reflects the fact that they were not developing a commercial product and were therefore unlikely to apply for marketing authorisation. Even non-commercial treatments, however, can be affected by the EMA's decisions; for instance, the approval of Holoclar means that other providers of limbal cell therapies will need to demonstrate that their approach is different enough that they can continue to use it instead of the licensed product (an issue I will return to later in this chapter). Unsurprisingly, then, any apparent inconsistency in the EMA's decisions can cause consternation even amongst non-commercial developers, and for those aiming to commercialise the treatment this is a crucial concern. Negotiations with the EMA then become extremely important, and some of my interviewees reported this being a collaborative process similar to that experienced with the MHRA; for instance, Interviewee 17 described a constructive dialogue with the EMA about the appropriate endpoint for his trial:

> "It's that kind of negotiation with the regulators ... which is, from both sides really, is what is clinically meaningful?" (INT17)

Others, however, experienced the EMA's requirements as restrictive and unhelpful; for instance, Interviewee 1 described being unable to use his preferred outcome measure because the EMA specified a different measure:

> "I think durable complete responses are what you really want … that would be my preferred option. [But] we had some discussions with the EMA about that, and they weren't all that happy. [They have] a sort of standard endpoint that they use." (INT1)

It seems, then, that the EMA's approach to evidence is somewhat conflicted, with it often adopting a nuanced and flexible approach, but also being restrictive and even inconsistent at times. The uncertainty this creates is one of the key challenges created by regulatory approaches to evidence in cell therapy trials, which I will now move on to explore in more depth.

7.4.2 Regulatory challenges for cell therapy trials

The most notable challenge for the regulation of cell therapies that I saw during my fieldwork was the difficulties caused by a lack of expertise amongst regulators about the treatments being regulated, as highlighted by a trialist giving a talk at a course on running cell therapy trials:

> "The regulators are on a learning curve as well - they're not a good fit for biological treatments that are living systems." (Field notes 01/05/14)

Another trialist speaking at the same course highlighted the problems that this inexperience can cause, explaining that regulators initially asked him for evidence about his treatment that, whilst being a standard request for a drug, was completely inapplicable to a cell therapy:

> "When I first spoke to regulators they wanted to know the exact chemical composition of my limbal culture." (Field notes 01/05/14)

Thus, the novelty of many of cell therapies, and the complexity of the science involved, means that the trialing process is new and unfamiliar territory for both

trialists and regulators. This can lead to significant uncertainty about what evidence will be needed and how it is likely to be interpreted, as explained by Interviewee 17:

> "Because there aren't that many tissue engineered products that have been through this kind of pathway, it's difficult to know what the regulators will accept, you know - to build up that kind of data pack to influence them, to persuade them that it's the right thing to do." (INT17)

The novelty of these treatments, then, means that cell therapy trials are not only encountering (and helping to resolve) clinical and scientific uncertainties, but also uncertainties in the trial regulations themselves.

Because the regulators are perceived to have so little expertise and experience, many cell therapy trialists were concerned that they might take a risk-averse approach and turn down anything that they didn't understand. For instance, Interviewee 7 described the difference between the regulation of a familiar treatment, such as bone marrow cells, and a more experimental cell therapy:

> "Everyone understands what you're doing with bone marrow cells - you might want to do something different, but fundamentally people understand what you're doing. But with [cell therapy being trialled], nobody knows. So if you ring up [regulator] and sort of say 'how do we take this forward?' they'll say, 'well just tell us what you're doing' … But they don't know you see, and so the easiest thing to do - which is always the safest thing to do - is to say no." (INT7)

The implication of regulators taking a risk-averse approach was highlighted by Interviewee 9, who explained that there was a danger they would ask for additional evidence which would be difficult and time consuming to generate:

> "When you're peer reviewing something people tend to be negative, and they tend to ask for more rather than less, particularly when they're uncertain themselves." (INT9)

This concern made him feel reluctant to proactively approach the MHRA with questions, worrying that this could cause unnecessary problems:

> "I didn't know how much to tell the MHRA up front … part of me was thinking, shall we just go and have a discussion with them, but part of me was thinking well the regulations aren't there yet - so the risk of doing that is that we know they're not going to understand our therapies as well as we understand them, so they may then ask us to do all sorts of things that we're not planning to do." (INT9)

It appears, then, that a perceived lack of expertise in a particular area might make trialists nervous about being completely transparent with regulators.

Despite these concerns, however, it seems regulators are aware that the novelty of many cell therapies means that they may lack the expertise needed to fully understand the treatment. This means that the MHRA, in line with their collaborative approach described above, appear to some extent to be willing to rely on the expertise and judgement of those submitting the application, as highlighted by this quote from Interviewee 9:

> "They fully admitted that … they know much less about this than we do, and so they have to be guided by what we tell them. And as long as there's nothing in the dossier which looks outrageously dangerous, they'd probably be happy." (INT9)

This approach is clearly necessary in an area where the science is both complex and fast-changing, and which is outside of the regulator's field of expertise, however it can also create issues for trialists who find themselves needing to negotiate and influence rather than fitting into a pre-existing framework. Large corporations tend to have extensive experience of influencing decision makers, and have the resources to do so successfully, but for the SMEs and academic sites conducting cell therapy trials the task is a daunting one, as highlighted by Interviewee 17:

> "It's such a huge organisation, the NHS - I don't know where, from our perspective as a small organisation, who do we interact with

> and where do we spend our valuable resources to influence and learn?" (INT17)

Interviewee 17 went on to explain that this was a main reason they might have to either give up on the treatment or sell it to a bigger organisation:

> "It might mean that we have to park that or sell the technology at that point to a large organisation who have the infrastructure to devote lots of time and resource to influence the right people." (INT17)

It appears, then, that although a flexible approach is valued by trialists, lack of certainty and the need to influence decision makers mean it can also cause them practical difficulties.

Another issue that my interviewees experienced when negotiating the regulatory framework was the variety of ways regulators might approach the concepts of similarity and difference. As I described in the previous chapter, the process of developing a cell therapy is an iterative one, involving making refinements to the treatment as new information is generated. Making such changes once the trialling process has started can cause problems, however, if the regulator sees the change as having created a fundamentally 'different' treatment, as highlighted by Interviewee 17:

> "I wouldn't like to have to start from scratch again just because we change a parameter, and there's a way we can rationalise and do some bridging work that can demonstrate that while there is a change it doesn't fundamentally change what we're trying to do. And I know that makes us slightly different, that we're asking for special review and circumstances compared to say a drug manufacturer or an antibody manufacturer, but I don't think many of these products will come to fruition unless there's that kind of degree of latitude to change." (INT17)

This quote highlights the need for evidence to prove that something is 'the same', but also the uncertainty around whether this will be accepted by the regulator. This is

another area which is complicated by the number of different organisations involved in decision making, all of which might approach such evidence differently. Again, this is highlighted by the case of ACI, where NICE treated three different products (ChondroCelect, MACI and the Oswestry method) as 'the same' for the purposes of its review, despite all having different cell manufacturing processes and costs. This means that accumulated effectiveness and safety data can be used to support each of the products, but it also means that ACI produced at NHS sites is being assessed for cost effectiveness as if the cost is the same as the commercial products, whereas in fact the NHS-produced product is actually much cheaper. In contrast, the EMA essentially treats these treatments as 'different', having given marketing authorisations to MACI and ChondroCelect, thus, in order to keep providing ACI in the presence of licensed alternatives, NHS sites must be able to argue that their product is 'different' from those produced under licence.

Uncertainty about the way that different institutions will respond to evidence was also apparent, and problematic, in my interviewees' views on the use of innovative trialling methods such as adaptive designs. For instance, Interviewee 17 had initially been keen to use an adaptive design, but was eventually put off because of the lack of consensus about how the statistical analysis would be undertaken:

> "We thought about that kind of design - we've different options of [treatment delivery] that we use, so the adaptive clinical trial design would be useful as well. How the statistics follow on with those is debatable though." (INT17)

In another example, Interviewee 7 explained that he was cautious about using newer statistical techniques instead of more established methods because he felt that they were not well-understood:

> "The trouble is you think, well why can't people be more imaginative? But I'm sitting there myself thinking 'Oh I dunno, I do understand that, these double-blind placebo-controlled trials, I understand exactly what it is, but I don't quite understand these. And anything that goes out, makes you suspicious." (INT7)

The interviews also raised other issues that could make adaptive designs problematic for many cell therapy trials; for instance, Interviewee 17 explained that his treatment was so experimental that there was insufficient background information already available to allow for a phased adaptive design. He was also concerned that an adaptive design involving a number of different arms would dilute the power of an already small sample:

> "It's difficult to get that 20 to 50 to 100-patient group together to do the trial in the first place, and if you start splicing it down to different arms you lose all the power you may have had." (INT17)

It appears, then, that although adaptive methods have the potential to solve some of the difficulties trialists experience with generating evidence, they might also add to these difficulties by creating additional complexity, uncertainty and inconsistency.

In his study of the development of cochlear implants, Blume argues that the widespread adoption of the therapy was enabled by the development of a consensus about what should count as evidence of effectiveness. He demonstrates that this consensus prioritised certain aspects of the therapy whilst sidelining others, concluding that "rather than consensus regarding use of the implant in children having been evidence-based, it was evidence that was consensus-based" (Blume, 2009). Blume is discussing a technology that has now achieved widespread clinical adoption, providing a retrospective account of how this stabilisation took place, but this process of consensus building can also be seen prospectively in the various negotiations regarding evidence that I have described in this section. Evidence can be mobilised strategically to position a therapy in a particular way to facilitate its development, for instance by demonstrating it is 'the same as' or 'different from' another therapy, and there are disagreements about the relative weight that should be afforded to different types of evidence, as shown by the ongoing debate about the cost effectiveness of ACI. The way that evidence is positioned can have fundamental implications for the development of a technology, and indeed my findings suggest that evidence might need to be deployed in different ways in different contexts in order to facilitate innovation. For instance, early in its development a cell therapy might need to be positioned as 'similar' to others in order

to gain regulatory approval for trials, but this positioning could prove problematic in other contexts; for example, evidence of 'difference' might need to be mobilised in order to continue providing a treatment for which another provider holds a marketing authorisation. Thus, the ability of various actors to promote particular forms or interpretations of evidence is an important factor in the way that these therapies develop, and the process of consensus building will be an important factor in stabilising their identities and shaping their potential for adoption.

The various ways that institutions approach the generation and interpretation of evidence not only have implications for the development of specific cell therapies, they also structure the way that evidence itself is conceived. Again, the case of ACI provides a good example of this, with the first draft of the new NICE guidelines being met with disappointment amongst various stakeholders, and the British Association for Surgery of the Knee (BASK) urging ACI users to make submissions to NICE during the final consultation (BASK, 2016). Thus, NICE's interpretation of what should count as evidence is contested, and it is urged to consider other, more experiential knowledge alongside more formal evidence in its assessment of cost effectiveness. Nevertheless, the initial assessment has created an accepted 'truth' about the therapy, which is that it is still experimental, and this then informs regulatory perspectives about the design of trials, shaping the evidence that will eventually feed into future decision making. This recursive regulatory loop is described by Cambrosio et al. (2006) when they argue that: "regulation generates results, raises questions and produces phenomena whose significance feeds back into the practices that are the subject of regulatory activities." In this context, it is particularly interesting that my findings suggest that regulatory decision making for cell therapies is often a collaborative process, involving both the regulatory agencies and the developers themselves. The flexible approach taken by the MHRA, made necessary by the complex nature of the science underpinning cell therapies, suggests that the production of evidence in this area requires the application of expertise and judgement rather than merely applying a pre-specified series of rules. Thus, although EBM promotes the use of 'evidence' rather than 'expertise' or 'experience' in clinical

decision making, my findings suggest that expertise is in fact firmly embedded in the process of creating the very evidence that is supposedly used in its stead.

7.6 Discussion

It appears that both the 'crude' version of EBM and a more nuanced approach to evidence have significant traction in the cell therapy field. Trialists themselves understand trials as a fluid, iterative process, in which there are many outcomes of interest, and many ways in which a result can be significant, and there is evidence that both the MHRA and EMA can take a flexible approach to the generation and evaluation of evidence. A more rigid application of EBM principles was also apparent, however, for instance in the negative reaction of some clinicians to any trial design that doesn't follow the standard drugs development model, and the widespread acceptance of even badly-designed or preliminary RCTs as being definitive proof of a treatment's efficacy. These conflicting approaches to the application of EBM principles can to some extent be understood in terms of the way that different domains approach the collection and interpretation of evidence: EBM, on the one hand, mandates a rigid, prospectively-defined process, whereas clinical and scientific research have traditionally taken a more fluid, iterative approach. Scientific research, in particular, appears to be very removed from the evidentiary expectations of EBM, which is perhaps unsurprising given that the focus of EBM has always been on clinical rather than scientific evidence. This is not problematic for drug trials, where the science and its clinical application are quite distinct, but, as we saw in the previous chapter, the successful development of cell therapies requires a much more coordinated approach between science and the clinic. This brings science into the heart of the clinical trial, so bridging the gulf between these two domains in terms of their approach to evidence is a crucial step in facilitating a more effective clinical trials framework for cell therapies, and indeed advanced bio-medical therapies in general.

Using Cambrosio's concepts of regulatory and mechanistic objectivity, we can see that both crude and more nuanced approaches are also apparent in the different positions that institutions take on the generation and interpretation of evidence. Mechanistic objectivity is clearly visible in the approach of the HTA, with its 'tick-box'

requirements, and of NICE, with its refusal to discuss evidentiary requirements in advance. The MHRA, however, appears to demonstrate more regulatory objectivity, with a focus on how the decision is made - a flexible, collaborative approach that ensures regulatory oversight without imposing a strict and rigid framework. This is clearly welcomed by cell therapy trialists, but it is not unproblematic - not least because of the fundamental imbalance between expertise, which is largely restricted to the trialists themselves, and power, which lies with the regulator. Flexibility also brings with it uncertainty, because in the absence of clearly defined rules it can be difficult to predict how the regulator will respond to a particular set of circumstances. The importance trialists place on personal relationships and communication, which engender trust and mutual understanding, suggests a way to overcome these challenges, but for this to be a sustainable model it must be integrated at an institutional level, and not embodied in individuals who can come and go. Another important factor is the resources (both economic and intellectual) required to navigate the complex regulatory framework, and to influence regulatory institutions. Such negotiations can be beyond many of the academic institutions and SMEs that are currently at the forefront of trialling cell therapies, which aligns with research that suggests larger companies are more likely to be successful when applying for marketing authorisation (Regnstrom et al., 2009). This suggests that while regulatory objectivity might be beneficial, in that it allows for a more nuanced approach to evidence, it is important to recognise that its outcomes are to some extent dependent on the relative power and influence of the actors involved the process.

The importance of negotiating with and influencing regulatory institutions highlights another important dimension of the different views of evidence described in this chapter: the evidence used in decision making cannot be separated from the social context in which the evidence is generated and the decisions are made. Every aspect of how evidence is defined and interpreted is negotiated; for instance, the aspects of trial design that are considered essential or expendable, the choice of outcome measures and the specification of what is considered a 'significant' outcome, and the relative weight that different institutions place on different types of evidence. All of these decisions involve a process of negotiation and consensus

building, not just about what the evidence *says* but also about what the evidence *is*. Although this process of consensus building is clearly a social one, that is not to say that my findings suggest that the resulting 'consensus-based evidence' is entirely socially-constructed. Clearly, however, is it not an entirely objective reflection of nature either. Rather, it must be understood as co-produced, the result of a mutually-configuring articulation between the scientific and the social.

This lends weight to the argument, put forward in the epistemic critiques of EBM discussed earlier in this chapter, that there is no reason to suppose that RCTs are always the most valid form of evidence. Given the logistical problems associated with conducting RCTs for cell therapies, this suggests that there is value in exploring other forms of evidence, whether from alternative approaches to trialling or by exploring the value of evidence from other sources. In the following chapter I will explore how this theme of co-production links the different dimensions of cell therapy trials discussed throughout the thesis, and reflect on how it could underpin a more nuanced, socially-robust approach to evidence.

8. Conclusion

This thesis has examined cell therapy trials from a number of different angles, providing a comprehensive and thematically-varied examination of the field. In this concluding chapter I will draw these various themes together by considering my findings in the context of the conceptual framework discussed in Chapter 1, exploring the various ways that the science and social order of cell therapies are co-produced through trials. In the second section of the chapter I consider the implications of my findings, beginning with a discussion of the extent to which the challenges faced by cell therapy trials are distinctive. I argue that although not necessarily a special case that warrants special treatment, cell therapy trials face distinctive challenges because of their differences from the drug trials the EBM model is based on, and I go on to make some recommendations about how a more socially-robust trials framework could address these issues. Such a framework, whilst not advocating any significant exceptionalism for cell therapy trials, would recognise their specific requirements and limitations, as well as the limitations of the EBM model itself. The chapter concludes with some suggestions for future research which would help support the development and evaluation of such a model, and with some final personal reflections on the future of the field. Before embarking on the substantive content of the chapter, however. I will briefly recap the main findings from my research, which form the empirical basis for the conceptual analysis and practical recommendations that follow. In the introductory chapter I posed four research questions, and here I summarise how these have been addressed by the empirical findings presented throughout the thesis.

RQ1 - How might the UK cell therapy trials landscape be characterised?

In Chapter 3 I described a UK cell therapy landscape that is small, fragmented and dominated by academic-led, publicly-funded studies. Most current trials are small and early-phase, and few are randomised or have more than two arms. There are very few trials of pluripotent cells, with haematopoietic and mesenchymal cells being the most commonly used, and only a third of trials involve a regenerative mode of action (and indeed many trialists actively distance themselves from terms such as

'regenerative' and 'stem cell'). The allogeneic-autologous distinction, which is used in much of the literature on cell therapy development, does not appear to be particularly significant for trials, where the complexity/risk of the procedure and the manipulation of the cells appear to be more important factors than the cell source. Most importantly, the fragmentation of the field means it is not possible to make generalisations about 'cell therapy trials' overall. In fact, each trial is much more affected by a specific set of local factors - including the clinical area, the specific treatment being trialled, and the context in which the trial is taking place - than by the fact that it is a trial of a cell therapy *per se*.

Whether the treatment is classified as an ATMP (and thus an IMP) is crucial to the logistics of running a trial, because CTIMPs require oversight by the MHRA, which significantly increases the cost and complexity of a trial. ATMP classification creates particular problems for trials run by academic units, which generally have limited experience of CTIMPs and therefore lack the skills and experience required to run such complex trials. This disconnect between the regulatory classification and the local context of trials leads to a distinctive set of social dynamics, which I explored further in Chapter 4. The policy environment is largely aligned with a commercial model of development, which conflicts with the reality that most cell therapy trials are academic-led. The relationship between clinical-academic and commercial development is an uneasy one, with economic realities encouraging a commercial mindset on the one hand, but conflicting priorities and values causing tension on the other.

The clinical-academic model of development also creates a distinctive relationship between research and care, because the clinicians involved have a very close relationship to the research. This is very different from drug trials sponsored by companies, where clinicians usually have a much more arm's length relationship to the treatment being trialled. Clinical-academic researchers being heavily involved means that there is less conflict between research and care, and to some extent this is reconciled by reconceptualising research *as* care, as clinicians attempt to develop treatments that will benefit their patients. Clinical cell therapy research, however, also creates new and additional challenges for care, because it often requires

significant investment and/or invasive procedures for the patient. In this context, the role of patient agency is crucial, and my research demonstrated a significant tension in cell therapy trials between protecting patients from undue risk whilst also allowing them to make their own decisions about the risks they are prepared to take. Cell therapies offer specific challenges in this area because the complexity of the science makes informed consent particularly difficult, and the hype surrounding the treatments increases the likelihood of therapeutic misconception.

RQ2 - What challenges are faced in the day-to-day running of cell therapy trials?

Inexperience of CTIMPs is one of the most significant challenges faced by cell therapy trialists. Academic units have traditionally not been involved in drug trials or late-phase trials, and the commercial enterprises involved in cell therapy trials tend to be small SMEs – often, in fact, university spin-off companies - which are equally inexperienced. The discussion of day-to-day challenges in Chapter 5 suggests that this is further exacerbated by the number of different domains involved in cell therapy trials. The complexity of cell therapies means that trials normally require input from basic scientific researchers, clinicians, cell manufacturing, pharmacy and evidence-based medicine, all of which are often unfamiliar with the specific requirements of either cell therapies or clinical trials.

Chapter 5 also highlighted financial constraints as a key day-to-day challenge for trials. The preponderance of publicly-funded and SME-led trials means that funding is often woefully inadequate for the needs of large, complex and heavily-regulated CTIMPs, and for publicly-funded trials this is often further exacerbated by difficulties securing reimbursement for the treatment itself. The amount of time required to undertake a trial is also an important challenge: the complex nature of cell therapy trials means there are many different factors that can cause delays, and changes in the regulatory structure or underlying scientific research during the trial only compound this. Finally, the nature of cell therapies themselves presents a significant challenge for trials. As living organisms, cell therapies do not lend themselves to the rigidity of a trial protocol, and the practical challenges of cell manufacturing can make the logistics of a trial extremely challenging.

Notably, these challenges tend to be localised and practical in nature, rather than being determined by centralised regulation: for instance, the problems some trialists experienced with excess treatment costs, and the challenges of aligning the work of the different domains involved in trials. Furthermore, whilst many challenges are very common, none appear to be universal, which suggests that the challenges faced by cell therapy trials are highly context-specific. It appears, then, that each cell therapy trial faces a unique combination of specific, localised challenges, further emphasising how difficult it is to generalise about this diverse, fragmented field.

RQ3 - How is uncertainty understood and managed in cell therapy trials, and how does this relate to uncertainty in the underlying science?

In Chapter 6 I described the various scientific and clinical uncertainties involved in cell therapy innovation, and highlighted the extent to which these uncertainties are interlinked. Clinical trials help to resolve these uncertainties in two key ways: *reverse translation*, whereby clinical testing generates information that helps to resolve uncertainties in the basic scientific research, and *learning through doing*, whereby actually treating patients helps to resolve clinical uncertainties, such as the therapy's mode of action, the logistics of clinical delivery and variability in patient response. The link between scientific and clinical uncertainty, and the importance of clinical trials for resolving both, is one of the most important ways that cell therapy trials differ from drug trials. Traditionally, by the time a drug reaches Phase 1 trials there is very little scientific uncertainty about the chemical compound itself, and the trialling process is mainly used to resolve clinical uncertainties - i.e. uncertainties about patient response. In contrast, cell therapies often have significant unresolved scientific uncertainties when they reach Phase 1 trials, and indeed trials may be the only way to resolve these uncertainties.

Although trials are clearly a crucial step in the process of resolving scientific and clinical uncertainties, their role in the innovation process is not uncontested, with differing opinions about the extent to which uncertainty should be accepted in the clinic, even in a regulated, early-phase trial. The need for trials to contribute to scientific as well as clinical progress is also problematic because it requires close collaboration between the clinical and scientific domains, which have very different

research cultures and values, and also because it does not necessarily align with the expectations of funders, who tend to treat 'basic science' and 'translational/clinical' as largely separate areas of research.

RQ4 - How is evidence conceived and used by the different stakeholders involved, and what implications does this have?

Most cell therapy trialists are supportive of the principle of clinical testing being conducted in a structured and regulated way, but in practice it is often challenging to meet the expectations of EBM. EBM prioritises certain aspects of trials, such as randomised control groups and blinding, that are problematic for many cell therapies. It also devalues other forms of evidence, such as laboratory research, clinical expertise and the experiential knowledge of patients, which are important for the development of successful therapies. In Chapter 7 I described the mutability of cell therapy trials, and in particular the contingency involved in assessing what counts as success. My research identified a number of examples of stakeholders acknowledging this mutability and adopting a nuanced approach to evidence. For instance, trialists often work within the confines of the trial protocol to create flexibility, and the MHRA takes a collaborative, flexible approach to regulation that acknowledges the specificity of a particular trial, as well as the regulator's relative lack of expertise. There were also examples, however, of a more rigid application of EBM principles, for instance in the mechanistic approach taken by NICE and the HTA, and in the negative reaction of some clinicians to trial methods that did not fit the standard RCT model. Inconsistencies in the way that different actors interpret evidence can also be problematic, with different agencies placing differing weight on the same evidence, and the results of individual RCTs being used as a definitive answer on the success of a therapy, with significant implications for its future development.

8.1 Cell therapy trials and the co-production of knowledge

The mutable, contextualised and contingent nature of cell therapy trials and the evidence they generate has been a recurring theme throughout this thesis, highlighting the various ways that clinical research is affected by social context.

Keating and Cambrosio's style of practice concept suggests that there is also value, however, in examining how cell therapy trials configure clinical practice and processes of knowledge production and innovation. The most visible way that trials configuring practice emerged in my research was through clinicians reconceptualising research *as* care. This was particularly noticeable in my observations of the ENABLE trial, where research was an integral part of the clinical unit's activities and was entirely integrated with the clinical care of patients. The ENABLE trial also demonstrated other aspects of the style of practice model, such as the presence of a statistician who was heavily involved with the clinical team, the work the team were doing to develop and validate metrics for assessing outcomes, and their awareness of the relationship between measuring these outcomes and the clinical care of the patient. Likewise, there were examples of cell therapy trials influencing the type of research that might be undertaken, for instance finding new ways to conceptualise patients and diseases, in order to better understand the treatment. And, of course, the reverse translation approach, and the close links between science and clinic that are so important for cell therapy trials, mean cell therapy trials significantly influence not only clinical but also *scientific* practice - both directly, by providing certain types of evidence that are not available from the lab alone, and indirectly, by structuring scientific research around that which can easily be used and/or tested in the clinic (such as MSCs).

It seems, then, that in some ways trials represent a new style of practice for cell therapies. There is, however, a crucial difference between my findings and the framework that Keating and Cambrosio describe, which is the fragmented and small-scale nature of cell therapy trials. The style of practice I witnessed during my observations of the ENABLE trial was largely limited to one particular unit, and in fact their approach was not even accepted by other surgeons in the same clinical area, let alone other areas using cell therapies. One of the key findings from my research is that cell therapy trials are extremely heterogeneous and tend to be linked to individual personalities or small teams, and specific local conditions. Each trial, or unit running a small number of trials, tends to act largely in isolation, almost reinventing the wheel with each new study. Importantly, there was little evidence of

common platforms and systems that create a momentum and framework within which trials take place almost as a matter of course, such as Keating and Cambrosio report for cancer trials. Instead, what appears to be emerging is a patchwork of disparate styles of practice that are specific to particular trialling sites and treatment types. This is reinforced by the fact that although there is a distinctive regenerative medicine community in basic science, most clinical trialists align themselves more with their clinical area than with 'regenerative medicine' or 'cell therapies' *per se*, and there is limited networking and collegiality for cell therapy trials that might foster the development of such platforms in the future. This is perhaps unsurprising given the wide variety of cell therapies being trialled and disease areas being treated, and suggests that even as the field expands it may never develop the kind of style of practice that is seen in oncology. For cell therapies, then, we might perhaps expect to see distinctive styles of practice developing at a localised level, and perhaps eventually more widely in particular clinical areas or particular types of therapy (such as immunotherapies), but it is unlikely that a distinctive style of practice for cell therapy trials overall will emerge.

One of the most notable fractures in the cell therapy trials style of practice is the division between the clinical-academic context of the majority of trials and the commercial model of innovation that underpins the regulatory and policy environment. This divergence is most visible in the emerging *institutions* of cell therapy trials, both those specific to cell therapies, such as the CGTC, and those that order knowledge production and innovation in medicine more generally, such as the EMA and the MHRA. The making of institutions, and the ways in which they construct and wield authority, is an important ordering instrument of co-production (Jasanoff 2004). A good example of the role played by institutions is Miller's (2004) description of the Intergovernmental Panel on Climate Change (IPCC), which was instrumental in repositioning climate change from a localised weather phenomenon to a globalised concern. There are echoes of this in the actions of the CGTC, which has positioned cell therapy production as a centralised commercial activity, potentially marginalising those treatments and sites currently using a localised clinical-academic manufacturing model. Miller also describes the way that the IPCC solidified its

authority by articulating a particular model of science in politics, according power to experts and expert knowledge as being politically neutral arbiters. Again, there are echoes of this in the field of cell therapies, both in the way that regulators defer to 'expert' scientific knowledge to make decisions in this complex and fast-changing field, and of course in the positioning of trials as the gold standard for generating neutral, 'scientific' evidence. The difference between this and Miller's description of the IPCC, however, is the fact that the institutional positioning of cell therapies involves the interaction of a number of different institutions – such as the MHRA deferring to expert knowledge, and the EMA and NICE treating trials as the gold standard of evidence. Co-production in cell therapy trials, then, can be understood as emerging from the assumptions and authorities invoked by a range of institutions, which interlock and mutually reinforce to produce a specific framework that promotes a commercial model. Clinical-academic innovation, in contrast, appears to exist in the liminal spaces of this interlocking model; lacking a cohesive institutional framework it struggles to gain or retain traction despite setting the agenda for the science and clinical aspects of cell therapies, and of course being the source of the very experts who are relied upon by the dominant institutional model.

Despite being a powerful institutional model, the regulatory framework does not generate clear and straightforward epistemic and practice-based requirements for trialists. For instance, trialists might be unsure about what evidence will be required by NICE when making commissioning decisions, or how the MHRA might respond to changes to a manufacturing protocol. The very classification of many cell therapies is even open to debate, with the ATMP definitions of 'substantial manipulation' and 'homologous use' being both subjective and reliant on scientific and clinical representations that are themselves uncertain. This plays an important role in the construction of social order for cell trials, for instance the classification (and thus regulation) of a particular treatment may have more to do with the success of particular interest groups in promoting their representation of it, as opposed to any inherent characteristics of the cell therapy itself. There is also significant uncertainty about the *future* of cell therapy regulation, which manifests in the 'anticipatory governation' I described in Chapter 5, whereby not only the existing

regulatory framework but also the predicted future framework impacts on the trajectories of innovation in cell therapies. Anticipatory governation can take different forms, such as the set-up of manufacturing facilities to meet expected future requirements, debates about how important it is to characterise cells in order to meet potential future evidence requirements, and flexibility being built into trial protocols to allow trialists to adapt to as yet unknown future conditions. Crucially, all of these actions are undertaken on the basis of *predictions* about what the future of regulation might look like, rather than certain knowledge. These predictions are of course inherently uncertain, and whilst they might be contested they cannot be disproved. Representations about the future of regulation can thus be seen not as a neutral and rational attempt to anticipate future regulatory demands, but as a means of establishing authority for a particular discourse or course of action in the present.

Anticipatory governation is a good example of how scientific uncertainty creates what Jasanoff and Wynne (1998, p.15) describe as "a domain of interpretive flexibility where competing social actors are free to appropriate and promote meanings associated with their policy interests." Another example of this can be seen in the uncertainties created by the fact that although at an overall level the various institutions involved in cell therapy trials present a relatively united front, at a more micro, interactional level there is actually significant variability between them. For instance, the HTA, the MHRA and NICE all adopt different approaches to flexibility and collaboration with trialists, and evidence may be treated differently in decisions by the EMA or NICE, or in decisions about different treatments. In navigating this landscape some cell therapy trialists adopt different *representations* of their treatment in different circumstances, for instance positioning it as 'the same as' or 'different to' another treatment. In constructing these representations they draw on the inherent uncertainties in the basic science, which allow for a myriad of different interpretations, none of which could objectively be deemed 'incorrect'. Here, then, rather than interpretative flexibility allowing competing actors to promote particular meanings to support their goals, individual actors are constructing a repertoire of meanings that can be deployed in different circumstances to further their interests.

Another manifestation of interpretative flexibility can be seen in the interaction of clinical and scientific uncertainty in cell therapy trials. Taking MSCs as an example, there are a range of conflicting representations of the cell themselves - for instance as stem/stromal/medicinal cells, as differentiating into certain types of cell, as well-defined, as unknown. These feed into different representation of MSCs in the clinic - as unknown, as risky, as safe, as 'working', as having wide applicability. Wynne (1992) argues that although science is often thought of as embracing uncertainty, in fact it attends to a specific range of 'tractable' uncertainties that are amenable to its methods - what Webster and Eriksson (2008) describe as the 'known unknowns'. Ignorance and indeterminacy are thus both endemic and largely invisible in scientific research, which focusses on resolving specifically defined uncertainties in specifically designed ways. Wynne argues that this only becomes problematic when scientific knowledge travels outside of science and is put to use in policy without consideration of these fundamental indeterminacies. The contested representations of MSCs in the clinic demonstrate the impact of this in practice: any attempt to invoke scientific authority in making clinical and regulatory decisions immediately uncovers the ignorance and indeterminacy involved in the basic science. Rather than providing neutral authority for a particular course of action, then, science in fact presents a range of different representations, again providing a repertoire of meanings to justify different paths.

The new uncertainties created by emerging biomedical innovations such as cell therapies raise important questions about which voices should be heard and prioritised in clinical decision making (Mesman 2008). The STS literature has documented a number of examples of patients increasingly becoming involved in setting the research agenda in specific clinical areas, for instance Rabeharisoa and Callon (2004) discuss the French Muscular Dystrophy association, which has promoted the active involvement of patients and their families in the production of knowledge, resulting in patients and clinicians "engaging in collective experiments, the remarkable effects of which is the mixing of lived experiences and laboratory results in the characterisation of MD." In comparison to this there appears to be a relative lack of traction for patient agency in cell therapy trials, which may be

explained by the fact that the FMD, like the other examples of patient involvement in co-production of evidence I discussed in Chapter 5, is disease-specific. Patient groups are inevitably concerned with understanding and treating a specific disease, rather than focussing on one particular kind of treatment, and indeed this is reflected in the way that cell therapy trialists tend to align themselves most strongly with their clinical area. However, cell therapy trials raise questions and uncertainties that cut across clinical areas, particularly about issues of trial design and access, the relative weighting of risks and benefits, and the issue of therapeutic misconception in a field characterised by both high expectations and complex, uncertain science. The fragmentation of the field and the lack of collective interest from patient groups may be making it more difficult for patients' voices to be heard about these uncertainties, giving greater weight to regulatory and scientific representations and less to the patients' lived experiences.

My research also highlights an important difference between the potential for *collective* agency, such as the examples of patient groups shaping the production of knowledge described in the STS literature, and the extent of *individual* agency available to patients in trials. There are thus two different levels at which patient agency must be evaluated and understood: patients might be able to shape the direction of research at a collective level, for instance by mobilising support for particular research agendas, but individual patients might still be denied agency because of the specific requirements of a particular trial, or indeed because their values and priorities differ from the collective patient view. For instance, eligibility criteria might be limited to patients who have exhausted all other treatment options, or to patients who are well enough to be considered low risk, or ill enough for the risk to be justified. Treatment protocols might demand a certain number of cells are grown in order for treatment to be administered, or limitations might be placed on the manufacturing process or type of cells that can be used, and of course if the cells are considered particularly risky the trial might not be approved at all. In all of these cases decisions are being made about an individual patient's care - weighing up risks and benefits, priorities and values – at a significant distance from the actual clinical decision and based on the risk assessment made by the regulator and the imperative

to generate 'valid' scientific findings, rather than the views of the individual patient. There are interesting parallels here to Michael and Rosengarten's (2012) account of PrEP trials for HIV prevention, which describes the conflict between ethical standards for trials, which demand the best possible care for trial participants, and the pursuit of statistical significance, which would require a high proportion of trial participants to be exposed to HIV infection in order to evaluate whether PrEP reduces the rate of transmission. Through a topological analysis they argue that despite their global enactment PrEP trials are profoundly localised, and they propose that "points (which might be entities or events) that are distant can also be proximal (categorically as well as spatially and temporally)". Although the empirical contexts are different, the divergence between individual and collective agency in cell therapy trials can be understood in similar terms: although patient agency might be mobilised at a collective (or global) level, it only acquires meaning and significance at a local (individual) level - i.e. the agency of individual patients to understand and make decisions about their own participation in trials.

If individual patient voices are marginalised by the ethical and scientific demands of trials, so too do clinical-academic researchers feel that their ability to make decisions on the behalf of, or in consultation with, their patients is diminished. In this context, the reframing of research *as* care can be seen as an attempt to give patients greater agency by providing them with access to potentially life-changing treatments which would otherwise be unavailable to them. Part of reconceptualising research as care involves clinician-academics constructing a specific *identity*, distinguishing themselves from the commercial sector and drawing authority from their position as 'care-giver' as opposed to 'profit-maker'. Framing trials as a way to care for patients positions them as an ethical clinical choice that justifies a level of risk that might otherwise be unacceptable. This is particularly noticeable in the positioning of cell therapies as akin to organ transplantation, which aligns them with a discourse of heroic medical innovation and life-saving technologies. Fundamental to this discourse is the implied assumption that in contrast to commercial priorities, which are inherently suspect, clinical experimentation is inherently ethical, and thus makes scientific uncertainty in the clinic 'acceptable'.

Just as science is often invoked as a neutral, a-political authority, here it is clinical necessity that is presented as objective and uncontested fact, invoked to provide ethical justification and legitimacy for a particular course of action. However, the absence of a commercial motive does not extinguish the potential for bias, self-interest and mistake, as was so visibly demonstrated by the Macchiarini scandal I discussed in Chapter 6. There is a wealth of STS literature highlighting the ways in which clinicians, and the trials they run, are affected by and affect their social contexts. The PrEP trials that Rosengarten and Michael (2012, 2010) describe were largely absent of commercial involvement, and yet their functioning and structuring of the environment they studied was far from neutral. Likewise, Sismondo (2008) shows that commercial bias in trials can be understood in behavioural terms rather than necessarily being conscious, deliberate and interest-based. The circumstances that foster this behavioural bias do not only occur in commercial trials; amongst other things, a close involvement with the treatment being tested, a genuine belief in its efficacy, and the motivation to generate 'significant' results for research funding and personal career benefits all create the circumstances for behavioural bias to occur in cell therapy trials.

Cell therapy trials, then, involve multiple intertwined uncertainties, allowing for multiple representations to be constructed and mobilised in the pursuit of particular interests. In this context, EBM can be seen as being deployed to control this uncertainty by providing neutral facts and processes on which to base decisions. Underlying this is the contention that EBM falls into the realm of 'science' rather than 'politics' (Marks 1997), but of course the idiom of co-production highlights the absence of a dividing line between the two. In her examination of 'regulatory science', Jasanoff discusses the blurring of the boundaries between science and politics that occurs when scientists become involved in policy-making (see for instance Jasanoff 1990, 2011). This blurring is very visible in cell therapy trials, with regulators relying on the input of scientists to make sense of the uncertainties, ignorance and indeterminacy of the field. The regulation of cell therapy trials is thus co-produced rather than being a separate entity to the trials themselves, and rather than EBM replacing the influence of 'expert knowledge' in decision making, it simply

moves it around – shifting it upstream from individual clinical decision making to more general and overarching decisions about trial design and regulation.

Another manifestation of the role of EBM in co-production is the role of protocols in cell therapy trials. Jasanoff and Wynne (1998, p.29) argue that legal proceedings and discourses are influential in "producing facts from uncertainty, in part through techniques of boundary work that demarcate regions of profound social and cognitive indeterminacy – and even cognitive dissonance – into domains of evidence and fact finding." Trial protocols can be understood as operating in the same way for cell therapy trials – by codifying, categorising and limiting the procedures of the trial, protocols attempt to control the complexity of the clinical and scientific context to enable stable facts to be created. However, the messiness and complexity of the context remain, resulting in the propensity for state-of-the-art trials to be "directed solely toward testing the efficacy of the intervention and not whether it will be effective in practice" (Michael and Rosengarten, 2012, p.98). This results in the value of the evidence generated by trials being understood by trialists and regulators differently, with trialists seeking contextualised, nuanced interpretations that will help them understand and develop the treatment, and regulators emphasising abstracted, neutral 'facts' that conform to the EBM hierarchy of evidence. In particular there is a start contrast between the value that EBM places on stable, unchanging and universal facts, such as a treatment 'works' or is 'safe', and the more iterative, incremental knowledge generation trialists value. This knowledge emerges not from the processes of the RCT, such as randomisation and blinding, but almost in spite of them. It is in fact more like a series of observations, generating very specific, situated accounts of cells and patients that feed into the ongoing construction of various representations of cell therapies. This process appears to be helpful in creating the 'porosity' between science and clinic that is seen as important for translational medicine (Martin et al., 2008, Wainwright et al., 2006, Brosnan and Michael 2014). However, it is often impeded rather than facilitated by trial protocols, and the linearity of the trials framework more broadly.

As well as being problematic for translational medicine, trial protocols also struggle to account for the complexity and uncertainty of clinical decision making for

cell therapies. This results in trialists building flexibility into protocols to give themselves room to manoeuvre in their care of patients, such as using ranges instead of thresholds for exclusion criteria or cell batches, thus again reintroducing a reliance on expertise and subjective opinion that EBM purports to replace. There is an interesting parallel here to Mesman's description of the subjectivity involved in using evidence-based clinical guidelines when deciding whether to opt for life-ending action during the birth of babies with a poor but uncertain prognosis. The guidelines for intervention set out different approaches depending on the categorisation of the child's condition, which suggests an objective decision-making tool that removes the decision from the immediate clinical situation and the expertise or experience of the particular treating clinician. However, as Mesman points out, the categorisation of the child's condition is in itself subjective, and the distinctions between the categories are vague. The decision about whether to treat or not therefore involves clinicians interpreting a range of observations and balancing various perceptions of risk and potential benefit, regardless of how 'evidence-based' or 'rational' the guidelines might be. Cell therapy trial protocols appear to function in a similar way, whilst on the surface corresponding to an EBM narrative about rational, objective decision making, they fail to account for, or control, the complexity and indeterminacy of actual clinical situations.

Miller (2004) argues that the idiom of co-production is useful for the "insights it provides into where knowledge-orders remain unconsolidated, tentative and fragile". It is therefore a particularly useful framework for examining the field of cell therapies, which is characterised by a conflicted, fractured style of practice where multiple identities, institutions, representations and discourses overlap, diverge, conflict and combine in various configurations and assemblages. The uncertainties of the field create a domain of interpretative flexibility which raises important questions about whose voices are and should be heard. In this context EBM is presented as an impartial arbiter, a scientific and a-political authority that can support rational, objective decision making in situations of great need and great uncertainty. Just as Knorr-Cetina (1999, 1977) describes the processes of the lab attempting to control and encircle the messiness of the natural world, so too do the protocols and practices

of clinical trials attempt to control the uncertainties of cell therapies in the clinic. However, the various themes explored in this thesis highlight the myriad ways in which trials and the evidence they generate are mutable, contingent and subjective – far from the neutral authority accorded to them. This contributes to the existing STS literature in two important ways. Firstly, it provides the first detailed empirical exploration of the 'doing' of cell therapy trials, and their role in the co-production of knowledge and social order in regenerative medicine. This extends and complements other STS research in the field, in particular Faulkner's concept of governation and the literature on the translational process. Secondly, it adds to the growing body of research on co-production, by exploring how the uncertainties inherent in new technologies present both conceptual and practical liminal spaces where representations and discourses can be mobilised in shifting ways. Most importantly, it suggests that exploring the emergence of multiple institutions, representations, discourses and identities, and examining the interactions and tensions between them, can provide a fruitful understanding of how science and social order are being co-produced in cell therapies. A third and important contribution of the thesis is that it suggests an approach for deploying the ideas and techniques of STS in an interdisciplinary way. By adopting a balanced ontological, epistemological and methodological standpoint, and engaging with perspectives from biology and health sciences as well as sociology, I have attempted to provide the foundation for a reconstructivist engagement with the policy of cell therapy trials. To this end I will now set out a series of concrete, practical recommendations, which emerged from and are grounded in the conceptual analysis above.

8.2 A more socially-robust model for cell therapy trials?

A number of important conclusions can be drawn from the account of trials and co-production presented throughout this thesis. Firstly, clinical trials of cell therapies are a mutable, contingent process that is heavily influenced by the social context in which the trial takes place. Secondly, the requirements of trialling have a structuring effect on innovation in the field. Thirdly, cell therapy trials are heterogeneous and context-specific, and it is unlikely that one coherent style of practice for such trials will

emerge. Finally, the trials framework is challenging for innovation in cell therapies, partly because many cell therapies are classified as drugs, which imposes a trials framework that is misaligned with the realities of many of the treatments, and also because this framework imposes a linear model which is out of step with the complex way in which innovation actually takes place. This goes to the heart of what is perhaps the most distinctive, and problematic, aspect of trialling cell therapies: the disconnect between the drug classification, with all of its implications in terms of commercialisation, regulation and evidence requirements, and the realities of cell therapies being living organisms that are largely being developed in an academic context. This is not to say, however, that cell therapy trials are unique - all of the challenges I have described in this thesis, such as the problems associated with excess treatment costs, or the difficulties of conducting trials involving surgical procedures, are experienced in other areas. Few areas, however, are likely to experience all of these challenges together - for instance, trials of surgical procedures share many of the design challenges of cell therapy trials, but the regulation of such trials is much less onerous because the treatments are not classified as drugs (Barkun et al., 2009). Likewise, many trials face challenges in terms of the length of time they take to do, and the recent case of Ebola highlighted the need for a more reactive trials process in times of crisis. Delays in drug trials, however, are problematic in times of clinical necessity, but they do not adversely affect the development of the treatment itself. This is very different to the situation I describe for cell therapies, where delays in the trialling process mean developments in scientific knowledge can make the results of a trial obsolete before it has even finished recruiting.

It seems, then, that cell therapy trials face a set of challenges that, whilst not unique in absolute terms, do appear to be distinctive in terms of their cumulative effect - a conclusion which supports Gardner et al.'s (2015) view that clinical trials present specific challenges for innovation. This does not necessarily mean, however, that the key tenets of EBM should be abandoned, and indeed none of the individuals I interviewed made any argument for cell therapies being a special case that warranted such an approach. Rather, there is an argument for a re-evaluation of the principles of EBM as they are applied in cell therapies, in the context of the wider

sociological literature which highlights the mutability of trials and the evidence they generate. My review of the main sociological critiques of clinical research in Chapters 4 and 7 demonstrates that it involves complex social and political processes, shaped by the myriad expectations, experiences and social interactions of those involved. These social processes mean that far from being the objective, neutral tools of EBM rhetoric, in practice the conduct of RCTs tends to be extremely flexible, adapting to specific circumstances on the ground (Sismondo, 2008). Rather than being a threat to the validity of the method, as a traditional EBM perspective might suggest, Will and Moreira (2010) suggest that methodological adaptability is in fact an essential feature of successful trials. In this final section I consider how this insight could be applied to cell therapies specifically, although in fact many of my recommendations will be relevant to other advanced therapies, and indeed more broadly to EBM overall. My recommendations break down into four areas: firstly, overarching points regarding regulation and policy that are relevant to all clinical research for cell therapies; secondly, specific points to consider in the design of cell therapy trials; thirdly, some thoughts on how 'off-trial' evidence could be approached; and finally, recommendations for further research.

8.2.1 General recommendations

Simplicity, consistency and flexibility in regulation

My research identified a number of aspects of regulation that are problematic for cell therapy trialists, most notably the classification of many cell therapies as drugs, necessitating highly-regulated clinical trials. Perhaps most important, however, are the challenges caused by complex, inconsistent and changeable regulations. Most of the individuals and institutions undertaking cell therapy trials are not experts or professional trialists; they learn from trial and error which is both time consuming and costly. Complex regulatory structures, and in particular substantial changes in classifications (for instance the introduction of the ATMP regulations) are destabilising and can significantly delay trials which are already facing other temporal challenges. Care should therefore be taken when making changes to the regulatory framework, because even an imperfect system, if it is simple and well-understood, could be more facilitative for trials than a complex system that frequently changes.

Finally, flexibility and collaboration are very important for effective regulatory oversight in this area, and it is important to invest in personal relationships and communication between regulators and trialists. Those undertaking trials should be encouraged by the facilitative approach of the MHRA, and opportunities to increase dialogue between them should be encouraged.

These regulatory and policy considerations are currently particularly important, given the implications of the UK leaving the European Union. Three aspects of EU policy are of most relevance to cell therapy trials: the Clinical Trials Directive, the ATMP regulations and the EMA. Leaving the EU provides an opportunity to adapt and improve these areas and address some of the challenges they pose for cell therapies. It is important, however, that this does not simply introduce more complexity and uncertainty, particularly because many cell therapies are being developed in conjunction with European colleagues, and many will require approval from the EMA. The aim of any regulatory change, therefore, should be to streamline, simplify and clarify regulations, and the benefits of being able to adopt UK-specific regulations must be balanced against the importance of maintaining consistency with the European framework.

A bio-clinical approach

Many of the challenges of cell therapy trials are either caused by, or contribute to, a disconnect between the different temporalities of clinical research, scientific research and technical innovation. The impact of this can be minimised, and the efficiency of clinical research increased, by ensuring that it interacts with and is responsive to scientific and technical developments. A bio-clinical approach should therefore be adopted wherever possible, whereby all clinical cell therapy research has both scientific/technological and clinical objectives from the outset. Such an approach can be encouraged by funders being more willing to accept, or even stipulating, basic scientific research in translational grants, and by ethics committees questioning the validity of any clinical research application that fails to address uncertainties in the basic science. In particular, ethics committees should take into account the amount and quality of scientific input for trials of particularly experimental and/or risky techniques, because a trial that is well-designed from a scientific perspective is more

likely to contribute to the eventual development of a successful clinical application, potentially justifying the greater level of risk involved. Conversely, trials that do little to resolve scientific as well as clinical uncertainties are less likely to contribute positively to the development of a treatment, making it much more difficult to justify any additional risk to patients. Ethics committees and funders could also encourage applicants to adopt a more EBM-like approach to scientific trial outcomes, for instance pre-specifying the analysis they will undertake, and ensuring negative results are published as well as positive. This would help to align the expectations of these very different research cultures, and aid in the review process by making it easier to assess and compare the quality of the proposed research.

Collaboration between different domains

Successful bio-clinical research requires the active input of scientists, clinicians and trial specialists, and also other domains including cell manufacturers and pharmacy. Good communication and understanding between these domains is crucial to the success of the research, and this should be encouraged and facilitated at both an institutional/policy level and for individual trials. One powerful way in which this can be done is the establishment of shared spaces, highlighted by (amongst others) Lyle (2016) and Ought and Bracken (2009) as a crucial element of interdisciplinary projects, and demonstrated by my own findings to be an important factor in breaking down the disciplinary barriers in cell therapy innovation. Alongside shared physical spaces can also be shared virtual spaces, whereby communication between domains can be facilitated by the creation and regular meeting of multidisciplinary teams for individual trials. Wider networks, most likely at a clinical level with a link to cell therapies, can also be used to facilitate this, creating wider platforms to underpin programmes of research.

A number of such shared spaces already exist: for instance, the ARUK tissue engineering network (a virtual space that connects clinicians, scientists, and manufacturers) and the MRC Regenerative Medicine Centre in Edinburgh, which is a physical space that brings together the various technical, clinical and scientific expertise required to successfully develop and trial new therapies. An important element that is so far largely missing from these initiatives, however, is the active

engagement of the trials community, and thus such initiatives should not only be encouraged and extended where possible, but should be extended to include trials specialists as a matter of course. Likewise, individual trials should be encouraged to have a multidisciplinary team that includes each of the key disciplines, including trial specialists, ensuring that all are active participants in the ongoing operational work of the trial.

Evidence interpretation

In addition to addressing the issues that make trials problematic for cell therapies, another important aim for regulation and policy should be the adoption of a nuanced approach to evidence that takes into account the social context and mutability of trials, and the limitations as well as the strengths of the EBM framework. For instance, as Cartwright (2010) argues, decision makers should look for a body of vouching evidence when assessing the potential of a treatment or the risk it presents, rather than prioritising the results of randomised trials. Techniques such as realist evaluation, which involves evaluating "what works for whom in what circumstances" (Pawson and Manzano-Santaella, 2012), provide a more nuanced approach to the evaluation of evidence than the rigid evidence hierarchies of EBM, and could be used as models for developing similar strategies for evaluating bodies of vouching evidence for cell therapies. Flexibility in the determination of what counts as good quality evidence is likely to result in more socially-robust decision making. For instance, if treatments are rejected for development funding, marketing authorisation or reimbursement on the basis of poor quality evidence (for instance because of the lack of a control group or blinding), because this type of evidence is logistically difficult or impossible to obtain, then innovation is inevitably skewed towards treatments that are able to generate certain types of evidence, rather than those that are most likely to be of clinical use. The quality of evidence about the safety and efficacy of cell therapies, then, might be better assessed against the type of evidence that is possible and/or most relevant for the particular treatment in question, rather than a generic hierarchy that assumes an RCT will always be the best quality evidence.

Patient agency

Respecting the patient perspective is perhaps the most challenging aspect of cell therapy trial regulation. On the one hand, my research suggests that it is important to give patients more agency in terms of trial participation and even design, but on the other hand it emphasises that it is particularly difficult to protect patients from risk in this area. This could be ameliorated in a number of ways, firstly by ensuring that patient and public engagement is a meaningful and ongoing process for every trial, rather than just a tick box exercise during the design and funding application stage. Secondly, there is a growing trend towards qualitative research being undertaken alongside trials, for instance interviews with patients during or after the trial, or ethnographic research during clinic visits, procedures and follow up visits. Such research helps to give context to quantitative results, and if made a standard part of cell therapy trials this would help to foreground the patient perspective, particularly if it is considered as part of the body of vouching evidence for a treatment and for the design of future trials. In particular, such research could be used to evaluate informed consent procedures, ensuring that the process is meaningful; this could include exploring how well patients understand the participant information sheet, how best to communicate any specific uncertainties or risks, and also the extent to which any particular terms (in particular 'stem cells') are likely to create unrealistic expectations. Such an approach could also be further developed to create a more generic consultative framework around informed consent that recognises the variety of ways that patients can interact with clinical research. Finally, it is important to consider which aspects of risk could be assessed by individual patients (for instance the extent to which other treatment options must have been exhausted), and which should remain in the hands of the trial team, such as any clinical factors that make the treatment unacceptably risky for a particular patient.

8.2.2 'On trial' evidence - a basket of tools

My research identified widespread support for the safety and efficacy of cell therapies being assessed in properly regulated clinical trials. There are, however, a number of factors that will have a bearing on the feasibility of specific aspects of trial design, and these should be taken into account both when designing a trial and when

assessing the quality of the evidence it generates. Figure 8.2 (overleaf) details the most important factors highlighted by my research, and the implications of these factors. This is not, of course, an exhaustive list, but is a good starting point when considering trial design. Importantly, many of these factors mean that the traditional drug designs may not be appropriate for a cell therapy trial. This is certainly not always the case, but in many situations trialists may have to look at other methods, and this should be accepted by peers if the standard RCT has been discounted because of valid reasons (i.e. it would not to be possible to conduct one in the future).

Taking into account the factors detailed in Figure 8.2, as well as the myriad of other factors that can determine the most appropriate trial design, it is clear that there is no one 'magic bullet' for cell therapy trials which will work in all circumstances. Rather, then, trialists need to have access to a variety of methods that can address the particular circumstances of their specific trial. It is out of the scope of this thesis to develop this 'basket of tools' in detail, but I can make a series of overall suggestions about certain techniques that either can be adopted or could be adapted to meet the needs of different cell therapy trials.

Adaptive methods

There are a number of adaptive designs that could offer some benefit for cell therapies, the three with the most potential being group sequential designs (which allow for different treatment options or combinations to be tested concurrently), enrichment designs (which allow for testing in a broad cohort of patients initially before progressively focussing on particular groups most likely to benefit), and sample size re-estimation, which allows for accumulating data to be used to change, and potentially reduce, the sample size as the trial progresses (Kairalla et al., 2012). However, all of these designs have limitations which mean they may not be

Figure 8.2 Factors affecting trial design and feasibility

Issue	Implication	Recommendation
Chronic vs. acute	Acute more likely to have problems with recruiting, and also with logistics of cells.	Care should be taken when planning trials in acute settings: – recruitment projections should be conservative – careful thought should be given to the informed consent procedure – particular emphasis needs to be placed on the local availability of cell manufacturing.
Invasiveness of procedure	The more invasive the procedure the more difficult it is to blind the study.	Consider sham procedures where possible. Where blinding is not possible avoid using patient reported outcomes as primary outcome measure as these are most likely to be affected by expectations. Where possible use assessments that can be done by a blinded assessor.
Length of outcome measure	Longer outcome measures may be necessary to fully understand effectiveness, but make trials longer to complete.	Investigate proxy outcomes Include validation work on correlations to inform future studies Work closely with regulators to discuss most appropriate approach.
Likely effect size	Larger effect sizes make for smaller samples, but also raise expectations.	Where possible power the trial for the smallest effect that would be clinically meaningful (i.e. not complete cure but any improvement). But where the treatment truly has the potential to cure, recognise that this could mean very small trials are reliable.
Potential dose response	Specifying particular doses risks patients being excluded from the trial if the cells don't grow.	Use ranges rather than thresholds for any prospective dose requirements. Where possible investigate dose response retrospectively through lab work linked to the outcomes, rather than prospectively
Alternative treatment options	Lack of alternative treatment options makes it difficult to have a control group. Also means patients may not have 'exhausted' other options before trying the trial.	Uncontrolled studies should be considered acceptable where no other acceptable treatment options are available Retrospective controls/case control etc. options should be used rather than no comparison. Exclusion criteria should give as much leeway as possible regarding alternative treatments used, as long as the PPI and consent procedures are adequate.

appropriate for the majority of cell therapy trials. Firstly, almost all adaptive designs require large sample sizes, and such numbers are likely to be impractical for many cell therapy trials. Secondly, adaptive designs are complex, require significant statistical and design expertise, and can be difficult and expensive to run, and are thus not likely to be suitable for the inexperienced academic units undertaking many cell therapy trials. Thirdly, in order for accumulating data to be used to adapt the design, the outcome measures (and in particular the primary outcome) must be relatively short-term. However, the majority of cell therapies require long outcome measures to properly test efficacy, so many trials would have finished recruiting before sufficient outcome measure data would be available to calculate any adaptations. Nevertheless, adaptive designs do present a useful option for the minority of cell therapy trials that have short-term outcomes, large samples and sufficient funding and expertise to use them.

Factorial designs

Factorial designs can provide an efficient way to assess the effects of two different aspects of a treatment within the same trial. This provides an alternative to adaptive designs for prospectively testing different versions of certain cell therapies, such as those that could potentially involve two combined elements (for instance the use of two different types of cells which might work separately or in conjunction), or the use of another procedure, such as a drug treatment or chemotherapy, in conjunction with the cell therapy. This offers the possibility of testing each element separately against each other and placebo, and of the two in combination - see Figure 8.3 (overleaf) for an example of how this can work. This method could potentially be adapted to be suitable for treatments that can be delivered in various ways, such as with a membrane or an injection, or for different dose options, avoiding the risk of reduced power when looking at different variations of the same treatment. This avoids the problems of adaptive designs requiring shorter outcome measures, but there may still be power issues if the trial is small, and there is a risk of diluting any treatment effect if one of the groups is less effective.

Figure 8.3: Example of a factorial trial design

		Chemotherapy	
		Yes	No
Cells	Yes	A	C
	No	B	D

A + B vs. C + D	Chemotherapy vs. no chemotherapy
A+C vs. B+D	Cells vs. no cells
A vs D	Chemotherapy combined with cells vs. placebo
A vs C	Chemotherapy combined with cells vs. cells alone
A vs B	Chemotherapy combined with cells vs. chemotherapy alone

Imbalanced randomisation

Every cell therapy trial should include a control arm if at all possible, even if this is not blinded and/or involves no treatment other than standard of care. Having an additional control group increases costs, however, or alternatively if the sample size is kept the same (thus avoiding increased costs) then the number of patients treated must be reduced in order to accommodate a control arm, thus reducing the information gleaned about the treatment itself. Imbalanced randomisation can address this to some extent, by making the control group smaller than the treatment group. Although this does result in a slight reduction in power, it is better than no control group at all, particularly for early-phase studies, and it maximises the sample size for the treatment group. Conversely, if excess treatment costs are a limiting factor then having a control group larger than the treatment group is a way to increase power without increasing the treatment costs.

Patient preference

Patient preference is difficult to address in trials, and there is no way to eliminate preference issues altogether. However, there are a number of methodological adaptations that can be used to minimise the effect of patient preference on the trial, and usefully these also allow patients fuller access to the treatment. A comprehensive cohort study, for instance, would randomise those patients who are indifferent about which treatment they get, whilst those who have a significant preference receive their preferred treatment and are followed up as an observational study. This could potentially be adapted as a way of having as many patients as possible followed up as part of a full study by having strict criteria for the randomised study and less strict for the observational - thus maintaining the precision of the main study, but also collecting as much information as possible. Another possibility that could be considered (although only in very exceptional circumstances) is Zelen's design, which involves randomising patients prior to their consent being sought. This avoids raising false hope for patients only to have it removed when they do not receive the new treatment, but of course there are significant ethical issues about randomising patients before consent. This may be appropriate in certain circumstances, however, particularly in acute settings where reducing the burden and complexity of the decision for the patient is an important factor. Again, all of these options are potentially complex from a statistical perspective, and therefore require the input of an experienced trials team.

8.2.3 'Off-trial' evidence - enhanced Hospital Exemption

The suggestions I make above, and indeed any other potential adaptations to trial design, have the potential to make some trials more efficient, but they by no means address all of the issues raised by my research, and they will not be appropriate for all, or even the majority of trials. Three particular challenges remain: firstly, problems associated with the overall utility of animal models will continue to present a challenge for cell therapies following a traditional drug trial phased approach; secondly, the linearity of the trials process, even if improved by more efficient trials, is still problematic for complex innovation; and thirdly, the designs I describe generally require advanced expertise in trial design, and are likely to be more

expensive and resource-intensive than traditional trials, both of which will compound the difficulties already experienced by under-resourced and inexperienced academic sites and SMEs attempting to conduct trials. There, appears, therefore, to be value in exploring other ways of generating evidence in addition to the traditional trial, particularly as there are many patients currently being treated 'off-trial' under the Hospital Exemption (HE). Under the current system there is little oversight or structured evaluation of either the treatment or the outcomes of these patients. This is clearly a missed opportunity to generate useful evidence, and also arguably problematic from an ethical perspective, because patients are being exposed to experimental procedures without the protection of GCP. A more structured approach to treating patients off-trial could thus provide both more robust oversight and an additional source of evidence to support innovation. Such an approach, which should aim to provide more oversight than the current framework but less than a full-scale trial, could be particularly useful for therapies being developed in a clinical-academic context - i.e. with no commercial aim - as these are the areas that are most likely to struggle with the commercially-aligned trials pathway and regulatory framework.

Underpinning the development of an enhanced HE framework should be an understanding that most cell therapies must be understood as 'complex interventions' for research purposes. The term complex intervention is generally understood as having two implications: firstly, that the intervention involves multiple, interacting components; and secondly, that the delivery and outcome is context-specific. Although the term is most often used to refer to interventions in mental health, policy and even education, it has also been used to describe the dynamics of innovation in surgical practice, which has clear relevance to the development of cell therapies. The methodological literature on complex interventions tends to emphasise the need for early development work to refine the intervention, which then feeds into clinical assessment. In particular, the IDEAL framework, summarised in Appendix 5, has been put forward as a means of increasing the robustness of evaluation for innovative surgical techniques (McCulloch et al., 2013; Ergina et al., 2013; Cook et al., 2013). It provides a useful platform for the regulation of such early development work and could be expanded and/or adapted to address the specific

characteristics of cell therapies, for instance the link with scientific research and cell manufacturing.

Key to the IDEAL approach is the use of randomised data where possible, with the addition of prospective observational methods either at the earlier stages of development or when randomisation is impractical or unethical. An enhanced HE framework, based on the IDEAL principles, would thus not be intended to replace 'proper' clinical trials, but rather would extend the methods of evidence generation available, particularly at the early stages of development. It could thus be used to supplement trials in two key ways: firstly, by providing robust, structured pre-trial evidence in circumstances where animal models are inappropriate; and secondly, by providing additional evidence alongside full trials, which would bolster the body of vouching evidence available to decision makers, and at the same time provide additional opportunities for learning in clinical practice, which will aid in the later stages of innovation and adoption. Three particular aspects of the IDEAL framework appear to offer particular promise for cell therapy trials: firstly, the use of prospective databases and registries instead of case series studies; secondly, comprehensive, pre-specified, reporting of the use of new techniques to ensure that both positive and negative outcomes are reliably reported; and thirdly, the use of prospective observational methods, such as interrupted time series, in situations where randomisation is not possible.

For such research to be successful it will need to align with the evidence generated by trials and meet the expectations of decision makers. The specific methods used will differ depending on the circumstances, but as a minimum I recommend that the following principles should be incorporated into any research conducted as part of an off-trial research programme:

1. Eligibility criteria can be much wider than an actual trial, but all of the variables related to eligibility must be documented so that the results can be interpreted fully. Particular care must be given to consideration of whether a patient would have been eligible for a trial or not, and the resulting impact on outcomes.

2. Consent procedures might not need to be as onerous as for a full clinical trial but should be more comprehensive than for surgery alone. Specifically, consent to the research aspects should be documented, and participant information sheets/informed consent processes should be adopted that ensure the patient is fully informed about the experimental nature of the cell therapy aspect of their treatment.
3. Data collection should be systematised and pre-specified, meaning there should be a documented plan for the data to be collected, which should include as many aspects of outcomes and follow-up as would be used for a trial. However, it is important to ensure that data collection does not place additional burden on clinical teams; one way to achieve this is to investigate ways in which routine data can be used in the measurement of outcomes, which is a growing field of research in trials methodology.
4. There should be documented plans for reporting and publication, with a commitment to publishing all outcomes, both positive and negative. Where necessary it should be possible to publish negative outcomes anonymously, and consideration should be given to how this could be done outside of the usual journal/peer review process.
5. The exact treatment used, including all aspects of the cell manufacturing and treatment protocol, must be recorded - this is essential if results are to be compared. This may cause problems for commercial treatments and raises the issue that this approach may only be appropriate for treatments being fully developed in a clinical-academic context.
6. Where possible all sites using cells for a particular indication should participate in a centralised process, rather than adopting individual approaches. This would ensure coordinated data capture and better coverage of all patients treated, and would also aid oversight by creating a central repository with easy access for regulators.

8.2.4 Recommendations for further research

The non-disciplinary approach I have taken has the benefit of producing a comprehensive account of cell therapy trials, and of being accessible and relevant to a broad range of stakeholders, including social scientists, policymakers, basic scientists, cell manufacturers and trial methodologists. However, as I discussed in Chapter 2, this broad applicability inevitably comes at the expense of depth in any one particular area. With this in mind, my findings suggest a number of discipline-specific themes that warrant further research, and which would help in the delivery of many of the recommendations I have made.

The patient perspective

My findings highlight the importance, and the difficulty, of addressing issues of patient agency in cell therapy trials, and whilst my methodology engaged with the patient perspective it did not actually involve any direct research with patients. Further research in this area, which lends itself to a sociological approach, would help to shed light on the way that patients experience and make sense of their involvement in trials of advanced, experimental biological therapies, and the various ways that trials, and the research framework more broadly, frame and are framed by the patient. In particular, such work would do well to explore and deconstruct key discourses of patient agency, such as Patient and Public Involvement, Patient Focussed Medicine Development and Patient Centricity, and how patients make sense of these supposedly empowering concepts. The concept of patient-led trials is a particularly interesting recent development, as it appears on the one hand to represent a shift towards a more patient-focussed approach to commercial trials, whilst on the other hand appearing to be an entirely corporate-led endeavour. For instance, a review of the website for a recent patient-led trials conference in London indicates that the vast majority of speakers were commercial representatives, with the remainder being from either academia or the NIHR. Not a single presentation appears to have been given by an actual patient or patient group, and the high

registration fee suggests that few patients or patient representatives would have been able to attend.[14]

Trials methodology research

A second important aspect of my findings that warrants further research is the lack of cell therapy expertise amongst the trial methodology community, particularly in the context of the need for a variety of methods that can be employed in different contexts and circumstances. Future trials methodology research should thus recognise the specificities of different types of cell therapies, and the likelihood of different methods being required for different types of therapy. I have mentioned a number of methodological options available at present that could be adapted to be better suited for cell therapies, including adaptive and factorial designs, realist evaluation, patient preference designs, the use of routine data and the IDEAL framework. Methodological research, including methodological reviews and modelling of different statistical techniques, would help to identify how appropriate these techniques would be for different types of cell therapies, and also how they could be adapted or combined to produce a comprehensive research framework that encompasses both on- and off-trial data.

Scientific research in the clinic

A third important avenue for further investigation, most likely involving a combination of scientific, sociological and health science/policy research methods, should be an exploration of ways to align scientific cell therapy research with clinical trials. Two particular issues suggest themselves as important areas of focus: firstly, an

[14] Notably, and perhaps unsurprisingly in these circumstances, many of the benefits the conference website claims for patient led trials relate to economic efficiencies rather than improved social outcomes for patients, for example:

> "When patients own trials, trials become more efficient, generate and retain volunteers, and deliver better outcomes."
>
> "Incorporating patient input from the outset to save costs in the long run."

examination of the differences between the research planning and reporting models used in science and EBM, with a view to developing best practice guidelines for 'bio-clinical' research. Importantly, such research would need to engage with the two domains' very different approaches to issues such as pre-specified protocols and outcomes, statistical analysis and significance, and the reporting of non-significant results. Secondly, a review of the way that NHS research ethics committees and research governance processes engage with scientific research, and in particular an assessment of the expertise and information required for health research oversight to have a meaningful role in assessing the scientific value of trials as well as the clinical benefits and associated risks.

8.3 Concluding thoughts

Few fields of human endeavour have created as much hope, as much hype, and as much controversy as stem cell research, which combines the promise of solving some of the most important healthcare challenges we face with the excitement of the almost god-like ability to create and manipulate life itself. We are, however, perhaps much further from realising these ambitions than the expectations raised would suggest; whilst the media hypes stories of scientists creating beating hearts in the laboratory, in reality the treatments that are closest to widespread clinical use are much more prosaic, providing little if any incremental benefit over and above existing treatments. The recent science has been peppered with 'breakthrough' moments - the cloning of Dolly the sheep, the isolation of hESCs and the development of iPSCs to name but a few - but the clinic still awaits a similar leap forward. It may be that recent successes, such as those seen in immunotherapy or the late Geoffrey Raisman's work on curing paralysis (BBC, 2017), will prove to be just such a moment, or it may be that the breakthrough will come from something as yet unknown, or not at all.

I make no judgement about whether the hype surrounding cell therapies is justified, or likely to be fulfilled. What does seem clear, however, is that the full clinical potential of cell therapies - whatever that may be - will only be realised if these experimental treatments are tested in patients. In these circumstances, it is

important to have in place a robust clinical research framework that both protects patients and facilitates innovation, and I hope I have demonstrated throughout this thesis the complexities and contradictions such a framework involves. But these difficulties do not mean the pursuit of robust evidence and oversight should be abandoned; rather, they suggest that there is value in reassessing the form that this takes, taking into account the specific characteristics of cell therapies. In their review of adaptive designs for clinical trials, Kairalla and colleagues (2012) conclude that "although ADs cannot 'change the answer' regarding the effectiveness of a particular treatment, they can increase the efficiency in finding an answer." My research suggests that a similar argument can be made regarding cell therapy trials: a more socially-robust approach to trials will not make ineffective treatments work, or inefficient products cost-effective, but it will maximise the chances of identifying those cell therapies that do have real clinical potential, and of developing them into workable, affordable treatments. I hope that my work goes some way towards showing what such an approach could look like, and in doing so supports the endeavours of all those who are working so hard to develop new treatments for patients in need.

Appendices

Appendix 1: Interview discussion guide

Introduction

- Discussion of the project's scope, aims and expected outcomes
- Confirmation of consent and willingness to be recorded

Details about the treatment and cell processing

- What is the treatment being tested? What is known about it so far?
- How are the cells processed? Who does the cell processing?

Details about the trial

- What methods are being used (randomisation, blinding etc.) Is there a full protocol available?
- Patient outcomes (official / unofficial)?
- Knowledge outcomes – how will it help them move forwards? Any work on looking at cell characteristics / biomarkers and outcomes? What is particularly important about this trial?
- Where was funding from? What role did the funder play in designing the trial (esp. choice of treatment protocols, cell processing etc.)
- Are there any other trials going on in this area? How about Hospital Exemption work? Any collaboration / shared knowledge?

Roles and responsibilities

- What is their role in the trial? Who else is involved?
- How does the trial function (team meetings, interim analysis etc.)
- Who was the main person driving the development of the trial? Who else was involved in decisions? Where does the impetus come from – is it clinic, science or both?
- Was advice available from a trials unit or research design service? Any involvement of CRN? And other support available?
- How do they relate to the concepts of 'regenerative medicine' 'stem cell research' 'cell therapy'? Do they perceive themselves as specialists in the disease area or specialists in cell therapy or regenerative medicine?

Challenges experienced

- What was their experience of the process of setting up the trial?
- Were there any specific regulatory obstacles because of use of cells?
- Any experience of designing other trials not using cells? How does this compare?
- Were there any logistical problems with use of cells? Any concerns / considerations to do with cost of delivery / scale-up?

Appendix 2: Interview information sheet and consent form

PARTICIPANT INFORMATION (DEPTH INTERVIEWS)

Clinical trials and the challenge of regenerative medicine

You have been approached to take part in a research project focusing on clinical trials in regenerative medicine. Before you consent to taking part, more information about the project, its funding body and projected outcomes are included in this information document. Please ask if there is anything which is unclear or you require any further clarification.

Purpose of the Study

The aim of this project is to investigate how clinical trials are used in the field of regenerative medicine, and in particular the area of cell therapy, and how the regulatory requirements of trialling are impacting on the development of the field. The research is being undertaken as part of a doctoral thesis.

Organisation and Funding

The research is being undertaken by Ruchi Higham, who is a PHD student in the Science and Technology Studies Unit (SATSU) at the University of York, which is located within the Department of Sociology, and has been established 25 years. The research is supervised by Professor Andrew Webster, who is Director of SATSU, and Dr Paul Genever, who is a reader in the Department of Biology at the University of York. The project is funded by the Economic and Social Research Council (ESRC).

Outcomes of the Project

The project intends to make an important contribution towards understanding how clinical trial regulations can be adapted to address the specific challenges posed by cell therapies. This will involve developing a detailed understanding of the specific challenges experienced by individuals and organisations attempting to design and gain authorisation for cell therapy trials. The research will also explore how innovative trialling methods, such as adaptive trials, could be used to address some of the issues currently being experienced.

Your Role in the Project

You have been approached as a participant in this project because of your involvement in the field of regenerative medicine, and your experience will help to advance our understanding of the clinical trials process in your area of expertise.

The Content of the Interview

What you are being asked to consent to is an informal interview where you will be asked about your work within the field. Broadly, this interview will cover the background of your work and how it has developed over time, any experience or knowledge of setting up and running clinical trials, any specific challenges you are aware of and how you think these could be addressed in future. Please feel free to elaborate on any answer or area which you think is particularly relevant or important. The interview will take approximately sixty minutes and will be recorded on a digital voice recorder (DVR) and later transcribed for analysis.

Ethical Approval

This project has been approved by the University of York's Ethics Committee. This Committee is satisfied that the following potential ethical problems have been addressed;

Consent
Attached to this document is a consent form, which you will need to sign before the start of the interview to acknowledge that you are aware of what the project is about and your role within it. You are free to withdraw this consent at any point before, during or after the interview, which will mean that any responses you have given will not be used during the data analysis. You are also free to refuse to answer any questions during the interview.

Confidentiality
All of your responses will be treated in the strictest confidence and will be completely anonymised so that anything you say cannot be traced back to you personally. In additional, any audio files from this interview will be destroyed upon completion of the research project.

Risk
The nature of this research presents little, if any, emotional or physical to you as a respondent. In the unlikely event that you are harmed by taking part in this research project, there are no special compensatory arrangements.

Contact Details

Ruchi Higham, SATSU
07881 308854
rh955@york.ac.uk

SATSU
Science and Technology Studies Unit

Thank you.

CONSENT FORM (DEPTH INTERVIEWS)

Clinical trials and the challenge of regenerative medicine

I confirm that I have read and understood the Participant Information document for the above study dated xxx and have been given the opportunity to ask questions.

I understand that my participation is entirely voluntary and that I am free to withdraw at any time without giving a reason.

I understand that I am free to refuse to answer any question during the interview.

I agree to the interview being recorded and later transcribed.

I understand that data from the project will be held securely for three years beyond completion of the project to allow for later papers to be produced.

I agree to take part in the above study.

We may wish to re-contact you at a later date to arrange another interview. Are you happy for us to do this? **YES/NO**

Participant's Signature: ...……

Participant's Name: ……

Date: ……

Researcher's Signature: ……

Researcher's Name: ……

Date: ……

Appendix 3: ENABLE information sheet and consent form

PARTICIPANT INFORMATION

Clinical trials and the challenge of regenerative medicine

You have been approached to take part in a research project focusing on clinical trials in regenerative medicine. Before you consent to taking part, more information about the project, its funding body and projected outcomes are included in this information document. Please ask if there is anything which is unclear or you require any further clarification.

Purpose of the Study

The aim of this project is to investigate how clinical trials are used in the field of regenerative medicine, and in particular the area of cell therapy, and how the regulatory requirements of trialling are impacting on the development of the field. The research is being undertaken as part of a doctoral thesis.

Organisation and Funding

The research is being undertaken by Ruchi Higham, who is a PHD student in the Science and Technology Studies Unit (SATSU) at the University of York, which is located within the Department of Sociology, and has been established 25 years. The research is supervised by Professor Andrew Webster, who is Director of SATSU, and Dr Paul Genever, who is a reader in the Department of Biology at the University of York. The project is funded by the Economic and Social Research Council (ESRC).

Outcomes of the Project

The project intends to make an important contribution towards understanding how clinical trial regulations can be adapted to address the specific challenges posed by cell therapies. This will involve developing a detailed understanding of the specific challenges experienced by individuals and organisations attempting to design and gain authorisation for cell therapy trials. The research will also explore how innovative trialling methods, such as adaptive trials, could be used to address some of the issues currently being experienced.

Your Role in the Project

You have been approached to take part in this project because of your involvement in a clinical trial which we are using as a case study. By understanding your experiences when setting up and running this trial we will be able to advance our understanding of the clinical trials process in stem cell research.

The Content of the Interviews

What you are being asked to consent to is an informal interview where you will be asked about your work on the trial. Broadly, these interviews will cover the background to your involvement in the trial, your experiences of setting up and running the trial, and any specific challenges you have faced and how you think these could be addressed in future. Please feel free to elaborate on any answer or area which you think is particularly relevant or important. Interviews will normally last around an hour, and will be recorded on a digital voice recorder (DVR) and later transcribed.

After this initial interview you may be asked to take part in one or more follow-up interviews at later points in the trial. You are under no obligation to do this, and you may withdraw your consent to participate at any time.

Observation at team meetings

In addition to your consent to be interviewed, you are also being asked to consent to a researcher observing some of the team meetings where the set up and/or running of the trial are discussed. The researcher will be there to observe only, and will not take part or ask any questions during the meeting. The meetings will not be recorded, but the researcher will take hand-written notes.

Ethical Approval

This project has been approved by the University of York's Ethics Committee. This Committee is satisfied that the following potential ethical problems have been addressed;

Consent
Attached to this document is a consent form, which you will need to sign before the start of the interview to acknowledge that you are aware of what the project is about and your role within it. You are free to withdraw this consent at any point before, during or after the interview, which will mean that any responses you have given will not be used during the data analysis. You are also free to refuse to answer any questions during the interview.

Confidentiality
All of your individual responses will be treated in the strictest confidence and will be completely anonymised. In additional, any audio files from the interviews will be destroyed upon completion of the research project.

It is important that you are aware, however, that the name of the trial used as a case study will not be kept confidential, and it may therefore be possible for some people who are familiar with your work to identify you as being a likely participant in this research. Because of this you will be given the opportunity to check all the research

outputs before they are submitted for publication, and will be able to remove anything that you feel may identify you or which you do not wish to be made public.

Risk
The nature of this research presents little, if any, emotional or physical to you as a respondent. In the unlikely event that you are harmed by taking part in this research project, there are no special compensatory arrangements.

Contact Details

Ruchi Higham, SATSU
07881 308854
rh955@york.ac.uk

Thank you.

CONSENT FORM (CASE STUDY)

Clinical trials and the challenge of regenerative medicine

I confirm that I have read and understood the Participant Information document for the above study dated xxx and have been given the opportunity to ask questions.

I understand that my participation is entirely voluntary and that I am free to withdraw at any time without giving a reason.

I understand that I am free to refuse to answer any question during the interview (if applicable).

I agree to the interview being recorded and later transcribed, and / or to notes being taken during team meetings.

I understand that data from the project will be held securely for three years beyond completion of the project to allow for later papers to be produced.

I agree to take part in the above study.

We may wish to re-contact you at a later date to arrange another interview. Are you happy for us to do this? **YES/NO**

Participant's Signature: ……

Participant's Name: ……

Date: ……

Researcher's Signature: ……

Researcher's Name: ……

Date: ……

Appendix 4: Trials dataset

Trial registry number	Status	Commercial funding	Clinical indication	Cell type	Cell source	Delivery	Mode of action	Phase	Sample size
UKCRN 11288	Follow up	No	Liver disease	Hematopoietic	Autologous	Procedure	Cell therapy	II	81
UKCRN 12108	Follow up	No	Rheumatological	Other	Autologous	Procedure	Immunotherapy	I	12
2010-021463-32	Recruiting	Yes	Gastrointestinal	Other	Autologous	Product	Regeneration	II	252
NCT01600755	Recruiting	Yes	Gastrointestinal	Other	Autologous	Product	Regeneration	I/II	30
NCT02064062	Set up	No	Other	Mesenchymal	Autologous	Product	Regeneration	II	10
NCT01606215	Follow up	No	Neurological	Mesenchymal	Autologous	Product	Cell therapy	II	13
NCT01898390	Set up	No	Neurological	Neural	Allogeneic	Procedure	Regeneration	I	40
NCT01151124	Follow up	Yes	Neurological	Embryonic	Allogeneic	Procedure	Regeneration	I	12
NCT02117635	Recruiting	Yes	Neurological	Embryonic	Allogeneic	Procedure	Regeneration	II	41
UKCRN3827	Suspended	No	Neurological	Neural	Allogeneic	Procedure	Regeneration	I	20
NCT01436487	Follow up	Yes	Neurological	Mesenchymal	Allogeneic	Product	Cell therapy	II	140
NCT01932593	Recruiting	No	Neurological	Hematopoietic	Autologous	Product	Cell therapy	I	6
NCT01815632	Recruiting	No	Neurological	Hematopoietic	Autologous	Product	Cell therapy	II	80

NCT00297193	Follow up	No	Gastrointestinal	Hematopoietic	Autologous	Product	Immunotherapy	III	48
NCT02166177	Recruiting	No	Gastrointestinal	Hematopoietic	Autologous	Procedure	Immunotherapy	I/II	26
NCT02327221	Recruiting	Yes	Gastrointestinal	Hematopoietic	Autologous	Procedure	Immunotherapy	II	160
NCT01175239	Recruiting	No	Immunodeficiency	Hematopoietic	Autologous	Product	Immunotherapy	I/II	10
NCT01380990	Recruiting	No	Immunodeficiency	Hematopoietic	Autologous	Procedure	Immunotherapy	I/II	10
UKCRN 12383	Recruiting	No	Cartilage disease	Mesenchymal and other	Autologous	Procedure	Regeneration	II	114
UKCRN 11523	Closed	No	Bone condition	Mesenchymal	Autologous	Procedure	Regeneration	II	60
2010-024162-22	Recruiting	Yes	Cartilage disease	Mesenchymal	Autologous	Procedure	Regeneration	I	10
NCT01795976	Suspended	No	Cancer	Hematopoietic	Autologous	Product	Immunotherapy	II	28
NCT01195480	Recruiting	No	Cancer	Hematopoietic	Allogeneic	Product	Immunotherapy	I/II	30
NCT01818323	Recruiting	No	Cancer	Hematopoietic	Autologous	Procedure	Immunotherapy	I	30
2011-001192-39	Recruiting	Yes	Cancer	Hematopoietic	Autologous	Product	Immunotherapy	II	60
2011-001788-36	Recruiting	Yes	Cancer	Hematopoietic	Allogeneic	Product	Immunotherapy	I/II	15
NCT01621724	Recruiting	No	Cancer	Hematopoietic	Autologous	Product	Immunotherapy	I/II	18
2008-006649-18	Suspended	No	Cancer	Hematopoietic	Allogeneic	Product	Immunotherapy	I	10
NCT01827579	Recruiting	No	Cancer	Hematopoietic	Allogeneic	Product	Immunotherapy	II	24

NCT01948180	Recruiting	Yes	Cancer	Hematopoietic	Autologous	Product	Immunotherapy	II	30
NCT02550535	Recruiting	No	Cancer	Hematopoietic	Autologous	Product	Immunotherapy	I/II	30
NCT02431988	Set up	No	Cancer	Hematopoietic	Autologous	Product	Immunotherapy	I	12
NCT02443831	Set up	No	Cancer	Hematopoietic	Autologous	Product	Immunotherapy	I	18
NCT00765453	Set up	No	Cardiovascular	Hematopoietic	Autologous	Procedure	Cell therapy	I/II	100
NCT01569178	Recruiting	No	Cardiovascular	Hematopoietic	Autologous	Procedure	Cell therapy	III	3000
2006-000280-28	Recruiting	No	Cardiovascular	Hematopoietic	Autologous	Product	Cell therapy	I/II	40
NCT01916369	Recruiting	Yes	Cardiovascular	Embryonic	Allogeneic	Product	Regeneration	I	9
UKCRN 4434	Follow up	No	Cardiovascular	Hematopoietic	Autologous	Product	Cell therapy	II	60
UKCRN 11185	Follow up	No	Eye disease	Limbal	Autologous	Procedure	Regeneration	II	20
2010-024409-11	Follow up	No	Eye disease	Limbal	Allogeneic	Procedure	Regeneration	I/II	20
NCT01469832	Follow up	Yes	Eye disease	Embryonic	Allogeneic	Procedure	Regeneration	I/II	16
NCT02129881	Recruiting	No	Kidney condition	Hematopoietic	Autologous	Product	Immunotherapy	I/II	12
NCT01977911	Recruiting	No	Other	Mesenchymal	Autologous	Procedure	Cell therapy	I/II	10
2012-001394-87	Set up	No	Skin condition	Mesenchymal	Allogeneic	Procedure	Cell therapy	I	10

Appendix 5: IDEAL framework for surgical innovation (McCulloch et al., 2009)

	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit; highly selected	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications (well defined)	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement; comparison	Comparison; complete information for non-RCT participants	Description; audit, regional variation; quality assurance; risk adjustment
Intervention	Evolving; procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT (efficacy trial); diseased based (diagnostic)	RCT with or without additions/ modifications; alternative designs	Registry; routine database (eg, SCOAP, STS, NSQIP); rare-case reports
Outcomes	Proof of concept; technical achievement; disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes	Clinical outcomes (specific and graded); middle-term and long-term outcomes; patient-centred (reported) outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No
Examples	NOTES video[6]	Tissue engineered vessels[7]	Italian D2 gastrectomy study[8]	Swedish obese patients study[9]	UK national adult cardiac surgical database[10]

RCT=randomised controlled trial. SCOAP=Surgical Clinical Outcomes Assessment Programme. STS=Society of Thoracic Surgeons. NSQIP=National Surgical Quality Improvement Program. NOTES=natural orifice translumenal endoscopic surgery.

Table: **Stages of surgical innovation**

Abbreviations

ACI	Autologous Chondrocyte Implantation
ATMP	Advanced Therapy Medicinal Product
CGTC	Cell and Gene Therapy Catapult (formally Cell Therapy Catapult)
CI	Chief Investigator
CRN	Clinical Research Network
CRO	Clinical Research Organisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
EBM	Evidence-Based Medicine
EMA	European Medicines Agency
ESRC	Economic and Social Research Council
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GvHD	Graft vs. Host Disease
HE	Hospital Exemption
HTA	Health Technology Assessment
hESC	Human Embryonic Stem Cell
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
iPSC	Induced Pluripotent Stem Cell
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MSC	Mesenchymal Stem Cell (or Mesenchymal Stromal Cell)
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIH	National Institute for Health (US)
NIHR	National Institute for Health Research (UK)
PI	Principal Investigator
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RM	Regenerative Medicine
RMEG	Regenerative Medicine Expert Group

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