Quality assessment of healthcare intervention studies in systematic reviews: improving established tools and approaches for context-specific assessments

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1 Abstract

Systematic reviews play an essential role in informing healthcare decision-making. A very important part of the systematic review process is an assessment of the quality of the included studies. This allows differentiation between studies which are methodologically robust and reliable, from studies which may have design weaknesses. Although quality assessment tools currently exist which are established and widely used, they nevertheless continue to develop and evolve.

The main aim of the publications in this thesis is to enhance quality assessment outputs. This should lead to improvements in the value and reliability of systematic review results and conclusions on treatment efficacy and safety. Some papers in the thesis propose improvements to established quality assessment tools: the Cochrane risk of bias tool for assessing randomised trials and QUADAS-2 for diagnostic accuracy studies. These ideas have had an impact. For example, evaluation of patient baseline characteristics has recently been incorporated into the next version of the Cochrane risk of bias tool to improve evaluations of randomisation process biases. Other papers relate to areas of healthcare research where a context-specific approach to quality assessment is needed i.e. where reliance solely on established tools may result in important issues being missed. These papers illustrate the importance of reviewers being aware of the *range* of issues which might affect the applicability (relevance) of a trial's results to other patient groups and settings.

Enhanced quality assessment outputs should provide systematic reviewers with a better understanding of study design issues. This should optimise systematic review recommendations for future research, by providing details of the important design issues which need to be addressed, together with suggestions for the most appropriate and viable study designs for future studies to consider.

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3 Author's declaration

The five papers included in the thesis are listed below along with my contribution to each. The integrative chapter that links the papers is solely my own work. 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.

Paper 1: **Corbett, M. S**., Higgins, J. P. T. and Woolacott, N. F. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Research Synthesis Methods*, 5, 2014, 79–85.

Candidate's key contributions: conceived the idea, prepared the manuscript and subsequent revisions

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Nerys Woolacott

Paper 2: Wade R, **Corbett M**, Eastwood A. Quality assessment of comparative diagnostic accuracy studies: our experience using a modified version of the QUADAS-2 tool. Research Synthesis Methods, 4(3), 2013, 280-6

Candidate's key contributions: conceived many of the ideas, co-wrote and revised the manuscript

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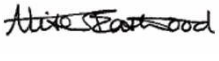
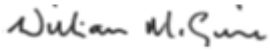
Mark Corbett

Signed: 

Alison Eastwood

Paper 3: **Corbett MS**, Moe-Byrne T, Oddie S, McGuire W. Randomization methods in emergency setting trials: a descriptive review. Research Synthesis Methods, 7, 2016, 46–54.

Candidate's key contributions: conceived the idea, developed the study design and coordination, identified studies, extracted and analysed the data, prepared the manuscript and subsequent revisions

Signed:  Signed: 

Mark Corbett William McGuire

Paper 4: **Corbett M**, Heirs M, Rose M, Smith A, Stirk L, Richardson G, Stark D, Swinson D, Craig D, Eastwood A. The delivery of chemotherapy at home: an evidence synthesis. *Health Services and Delivery Research*, 3(14), 2015, 1-182.

Candidate's key contributions: Led on nearly all aspects of the report which related to the review of clinical effectiveness (this publication covered a large, multi-component study).

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Mark Corbett Alison Eastwood

Paper 5: **Corbett M**, Watson J, Eastwood A. Randomised trials comparing different healthcare settings: an exploratory review of the impact of pre-trial preferences on participation, and discussion of other methodological challenges. *BMC Health Services Research*,16(1):589

Candidate's key contributions: conceived the idea, developed the study design and coordination, identified studies, extracted and analysed the data, prepared the manuscript and subsequent revisions.

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4 Introduction and context

Systematic reviews play an important role in informing healthcare decision-making by identifying, evaluating and summarising the best available research evidence on treatment effectiveness and safety. A key aspect of the systematic review process is assessment of the 'quality' of individual studies. In the context of healthcare evidence there is no universally accepted meaning of 'quality assessment', and it is sometimes used interchangeably with terms such as 'validity assessment' and 'critical appraisal'. The term 'quality assessment' is often used without further definition to allow the reader to differentiate what 'quality' is being assessed. A study's quality has been described as a multidimensional concept that could concern the risk of bias, quality of reporting, ethical approval and external validity.[1] Study quality might also cover adequacy of statistical analyses and conflicts of interest.[2] Furthermore, the term 'quality' has also been used for broader, evidence-base level evaluations ('quality of evidence') as seen with the GRADE system, though again its meaning is not defined.[3] This thesis focusses on methods for assessing the quality of *individual* studies.

Many clinical trials are not well-conducted. An oft-cited 1994 BMJ editorial on "*the scandal of poor medical research*" lamented that:[4]

"*Huge sums of money are spent annually on research that is seriously flawed through the use of inappropriate designs, unrepresentative samples, small samples, incorrect methods of analysis, and faulty interpretation. Errors are so varied that a whole book on the topic, valuable as it is, is not comprehensive*"

This quote encapsulates the broad range of issues that systematic reviewers need to be aware of when evaluating a study's quality. Considering the relevance and value of systematic reviews in informing healthcare policy, practice and future research[5-7] it is difficult to overstate the importance of study quality assessments within the systematic review process, particularly given that research waste is *still* considered to be a scandal.[8]

The results of quality assessments should facilitate differentiation between studies which are methodologically robust and reliable, and studies which may have design weaknesses or limitations. Such distinctions are critical to ensuring the most appropriate review conclusions and recommendations are made, since poorer quality, or biased, studies are known to produce estimates at variance with studies considered to be unbiased.[9]

Since the 1980s many quality assessment tools for clinical trials have been developed and published.[10, 11] Most tool components relate to either a study's 'internal validity' or 'external validity'. Internal validity components evaluate the degree to which a study is free from bias. Differences in the extent to which studies are affected by bias can help explain variation in the results of studies included in systematic reviews, with more rigorous studies being more likely to have results that are closer to the truth.[12] Consequently, many tools focus on aspects of internal validity. External validity (often referred to as 'applicability' or 'generalisability') has many components but has been broadly described as the extent to which a study's results may be extrapolated to a definable group of patients in a particular clinical setting.[13] A small number of quality assessment components relate to neither internal nor external validity. For example, the use of sample size calculations or whether ethical approval has been obtained.

Most of the older quality assessment tools are either checklists, or quantitative scales.[10] When quality assessment scales are used each individual component is scored, resulting in a single summary quality score. Examples include the Jadad scale[14] and the PEDro scale.[15] However, problems were noticed with these types of approach; the number and content of items assessed varied widely and developers often did not provide details of how and why component items were included.[10] Further concerns arose from the findings of a study which examined the association between treatment effects and summary quality scores. The study applied 25 different quality assessment scales to all 17 trials included in a published meta-analysis. Meta-regression analysis found that none of the 25 scales yielded a statistically significant association between summary scores and effect sizes.[16] Since it is known that biased trials are, on average, associated with exaggerated treatment effects[9] this result suggested that summary scores are not adequate for detecting bias. This study's results also showed that the type of scale used could dramatically affect interpretation of study quality. This is likely to be a consequence of tools not having adequate content validity and reliability and of using different weights/scores for particular components. Systematic reviewers were therefore faced with the problem of which tool to use.

These concerns led the Cochrane Collaboration to bring together statisticians, epidemiologists and systematic reviewers in 2005 to develop a new tool (the Cochrane risk of bias tool) for evaluating RCTs, which used a domain-based approach. Here, the focus was on determining internal validity, or risk of bias ('risk' was considered appropriate because the results of a study may in fact be unbiased despite a methodological flaw)[12]; quality assessment items relating to

external validity were excluded from the tool. Domains of bias were chosen based on empirical evidence and on theoretical considerations where evidence was scarce. The biases identified were then grouped into domains and guidance provided on how to make judgements on risk of bias. Furthermore, with the aim of improving process transparency (compared with earlier tools), users were encouraged to provide judgement reasons (including quoting key text from publications). The tool was published in 2008, with subsequent minor modifications published in 2011.[12, 17] Systematic reviewers adopting the tool now had a means of transparently reporting risk of bias assessments using a tool which was (at least partly) evidence-based, and which did not rely on a summary score.

The downside to this development was the focus only on risk of bias, at the expense of trial external validity issues. Formal evaluations of external validity are rarely undertaken in systematic reviews, although discussion of aspects of applicability is common. Nevertheless, lack of consideration of external validity is a frequent criticism by clinicians of RCTs, systematic reviews, and guidelines.[13, 18] External validity is not considered to be easy to assess, having been described as a "*slippery*" concept in which understanding depends on a detailed knowledge of the particular clinical condition being studied and its management.[19] Although several frameworks have been published for assessing external validity there seems to be little evidence of their perceived usefulness amongst decision-makers or other potential users.[20]

The Cochrane risk of bias tool is now probably the most frequently used tool in systematic reviews of RCTs.[21] Domain-based quality assessment tools for other study designs - such as QUADAS-2 for diagnostic accuracy studies - have also been developed, which similarly confer benefits over older tools.[22] Nevertheless, some limitations remain, and existing tools must continue to develop. A key problem is that all tools inherently rely on specific information being adequately reported in study publications. Despite the wide acceptance of the need to use reporting standards guidelines - such as CONSORT for RCTs[23] and STARD for diagnostic accuracy studies[24] - adherence is still sub-optimal, meaning that quality of reporting remains an important barrier to determining study quality in a systematic review.[25, 26]

A factor which is infrequently considered in systematic review quality assessments is the potential impact of chance effects, which can result in false-positive or false-negative trial results. These can arise when the number of outcome events are small, or when there are random baseline imbalances in important patient

characteristics. Chance effects are more likely to occur when trial sample sizes are small. If they are not identified they may become particularly problematic in reviews where meta-analysis is not viable. Chance effects are not usually evaluated in systematic reviews since they are neither a bias nor an issue of external validity. However, this should not mean that their impact should be ignored when considering the plausibility of trial results.

This thesis presents publications which improve and augment approaches to study quality assessments in systematic reviews. In doing so the thesis aims to highlight two reflections on my experiences of performing systematic review quality assessments. The first is that, despite recent advances, established quality assessment tools should not be considered as fixed but should continue to improve, with reviewers playing a key role in their development. The second is to highlight the importance of considering approaches to quality assessment based on the context of the particular review in question. Although the use of established quality assessment tools in some situations may be perfectly adequate - particularly where the intervention is simple - such a 'one size fits all' approach can sometimes result in important aspects of study validity being missed. These will often relate to the applicability of study results where interventions are more complex, since complex interventions may work best when tailored to local contexts rather than being completely standardised.[27]

The main aim of the publications is to enhance quality assessment outputs. This should lead to improvements in the value and reliability of systematic review results and conclusions on treatment efficacy and safety. Another aim is to improve review recommendations for future research – more useful and detailed recommendations should follow when reviewers have a better understanding of study quality issues.

5 Improving established quality assessment tools

5.1 Modifying Cochrane risk of bias tool judgements on selection bias

The Cochrane risk of bias (RoB) tool is very widely used in systematic reviews of RCTs.[21] Bias is defined by the tool's authors as 'systematic error or deviation from the truth in results or inferences'.[17] One of the several types of bias assessed is selection bias (see Table 1 in Paper 1[28]). This occurs where there are systematic differences between trial intervention groups in factors which affect response to treatment or prognosis. Paper 1[28] proposed a modification to improve the accuracy of selection bias judgements.

The RoB tool selection bias domain involves assessing the adequacy of randomisation, specifically the methods of sequence generation (i.e. whether or not this was truly random) and treatment allocation concealment. Judgements on each of these aspects of the randomisation process are categorised as 'high', 'low' or 'unclear' risk of bias.[17] Selection bias may have several causes but it usually occurs when trial investigators preferentially allocate certain types of patient to one intervention over another. This bias can be intentional or it may occur unwittingly. Although methods exist which can vastly reduce the risk of selection bias - such as centralised randomisation systems like interactive voice response systems (IVRS) - these are often not used, or the technology was not available at the time of the trial.

Identifying the need and opportunity for change

The impetus to modify the Cochrane RoB tool arose from experience of the generally poor reporting of randomisation methods in trial publications, resulting in many 'unclear' risk of bias judgements.[29] The need for a change was further illustrated by a Cochrane review on the completeness of reporting of randomised trials. It found that allocation concealment methods were reported adequately in 45% (393/876) of trials in CONSORT-endorsing journals and in only 22% (329/1520) of trials in non-endorsing journals.[25] 'Unclear' risk of bias judgements diminish the value of a trial to a systematic review by raising uncertainty about the reliability of its results. Consequently, in reviews with numerous trials with an 'unclear' risk of bias, the review results, conclusions and implications for practice will also be subject to uncertainty, frustrating reviewers, patients, clinicians and policy makers alike.

Paper 1[28] proposed a method for improving the accuracy of selection bias judgements by utilising additional information which might indicate more accurately how adequately randomisation was performed: patient group baseline

characteristics data. This seemed an approach worth exploring since the purpose of randomisation is to produce comparable groups (although it does not guarantee comparability).

The innovation involves bringing baseline assessments into the RoB tool and using them to inform, and hence improve, selection bias judgements. Although a minority of Cochrane reviews (around 9%) have assessed baseline imbalance in the past - via the 'Other bias' domain of the tool - linking those assessments with selection bias judgements is uncommon.[28] In using the modified tool proposed in Paper 1[28] decisions have the potential to be more accurate, since they would be made based on more sources of information i.e. what the randomisation methods seemed *likely* to achieve (methods details) plus what was *actually* achieved (baseline characteristics). Encouragingly, baseline characteristics are much more frequently reported than randomisation methods; the aforementioned Cochrane methods review reported that baseline data are reported in 95% of RCTs published in CONSORT-endorsing journals and in 87% of RCTs in non-endorsing journals.[25] However, these statistics are limited since they do not indicate how comprehensive the reported baseline data were, which is key to implementing Paper 1's[28] methods in practice.

The idea of using baseline data to inform judgements on selection bias relies on the existence of a sufficient knowledge base - or preferably evidence base - on important prognostic factors and treatment effect modifiers (sometimes termed 'predictors of response' or 'subgroup effects'). The difference between prognostic factors and effect modifiers is that prognostic factors relate to disease natural history and are independent of treatments, whereas effect modifiers are characteristics which are associated with a higher or lower treatment effect with a *specific* treatment.[30] A prognostic factor can also be an effect modifier. As most diseases have been extensively studied, sufficient knowledge of prognostic factors would be likely in many reviews via literature searches and clinical expertise within the review team. Such knowledge may be limited in new areas of healthcare research, though this same lack of knowledge might also make it difficult for trial investigators to introduce meaningful selection bias. When using baseline data to inform selection bias judgements it is preferable that prognostic factors and effect modifiers are pre-specified in review protocols. This would benefit reviews in other ways by informing decisions on approaches to subgroup analyses and external validity assessments (see section 6.2).

Using the modified risk of bias tool

Table 2 in Paper 1[28] summarises the framework developed on how risk of bias judgements should change when randomisation methods *and* baseline data are used to make decisions. One of the easier modifications described in Table 2 is the conversion of 'unclear risk' to 'high risk' judgements; an important imbalance in just one key characteristic would be enough to warrant a 'high risk' of bias judgement, and there is evidence to support this being a valid approach. A meta-epidemiological study of 23 trials of atypical antipsychotics in dementia patients found that baseline imbalances were associated with differences in efficacy estimates (e.g. higher mean age with a greater reduction in neuropsychiatric symptoms).[31] The meta-epidemiological evidence of exaggerated effect estimates associated with inadequate/unclear randomisation methods (which has been studied far more than the impact of baseline imbalance and statistical adjustments) is also relevant, since baseline imbalance is the mechanism by which such bias occurs.[32] However, review-specific consideration must be given to what constitutes an *important* imbalance. These should be assessed using levels of clinical significance rather than statistical significance[33] and should involve expert clinical advice, and (where available) published evidence e.g. 'minimum clinically important differences'[34] (MCID) which exist for some continuous outcomes. Baseline differences well above a MCID, or which are highly statistically significant, are likely to indicate the presence of very important bias. In this respect baseline assessments might also allow determination of the likely *extent* of bias on trial results. Where trial durations are quite short, and the disease course is stable in the short-term, the impact of any effect modifiers are likely to be more important than prognostic indicators of disease natural history (which might only become important for results from longer-term follow up).

Conversion of 'unclear risk' to 'low risk' judgements is likely to be more difficult to achieve, since systematic reviewers would need to have identified all known important prognostic factors and effect modifiers. A changed judgement could only be considered if baseline data were available for all factors; decisions should be made and justified commensurate with the evidence available on important baseline characteristics. For example, in a review of biologics for psoriatic arthritis[35] which I led, we were confident that all important effect modifiers had been identified because a recent systematic review of predictors of treatment response was available.[36] The availability of such high-level evidence may be quite rare though.

Incorporating the modification into version 2 of the RoB tool

The methods in Paper 1[28] are being used by researchers internationally – the paper has been cited in over 40 reviews and protocols (as of December 2018). To further disseminate Paper 1[28] I gave an oral presentation of the framework at the 2013 Cochrane Colloquium[37] and was subsequently invited to join the Cochrane Risk of Bias Tool Working Group, which was developing version 2 of the tool.

In version 2, randomisation methods together with baseline assessments will be used to evaluate selection bias under a re-named domain: 'Bias arising from the randomisation process'. Not all the proposals in Paper 1[28] have been incorporated into version 2, which is not unexpected given that a consensus approach is important for the widespread adoption of any proposed modifications. From discussions with other methodologists and researchers at a RoB tool Working Group meeting it was evident that while there was confidence in using baseline assessments to help identify likely bias (i.e. converting 'unclear risk' to 'high risk') there was reluctance to advocate using baseline assessments to rule out bias (converting 'unclear risk' to 'low risk'), as this was thought only occasionally to be practicable because there would likely be insufficient evidence on prognostic factors and effect modifiers. Consequently, the question on baseline imbalance in version 2 of the tool reads: "Did baseline differences between intervention groups suggest a problem with the randomisation process?"[38] However, opinions on this do differ amongst methodologists, as illustrated by one of Paper 1's peer reviewers who had the opposite opinion, considering that a strong statement of 'low risk' of bias could be made when randomisation methods are unclear but there are no differences in important factors (provided all are reported). The peer reviewer instead had some concerns about making 'high risk' judgements based on important baseline imbalances when randomisation methods were unclear, arguing that the imbalances could be due to chance.

How to handle chance baseline imbalances

Baseline imbalance in one or more important characteristics may be due to selection bias or due to chance. The identification of imbalances thought to be due to chance, as suggested in Paper 1,[28] will not be incorporated into version 2 of the RoB tool. Although this omission is logical - since chance effects are not caused by bias - it may leave reviewers with a problem where trials describe sound randomisation methods yet report an important unadjusted baseline imbalance. These studies will be classed as having a 'low risk' of bias even though the reviewer may have concerns about whether the trial's results are believable. It is therefore advisable that imbalances thought to be due to chance are noted during

risk of bias assessments (but outside of the RoB tool) and taken into consideration when results are synthesised.

Imbalances due to chance may be difficult to distinguish from those caused by selection bias. For trials describing methodologically robust randomisation methods which also have an important baseline imbalance, it would seem reasonable to conclude that the imbalance was likely to be due to chance. However, opinions differ on what constitutes methodologically robust randomisation methods. The Cochrane Handbook of Systematic Reviews - which provides guidance on how to use the risk of bias tool - says that the use of sequentially numbered, opaque sealed envelopes (SNOSE) to conceal treatment allocations carries a low risk of bias.[12] However, in practice, the bias risk is only lessened when those with access to the envelopes are distinct from those recruiting participants.[39] A study of allocation concealment methods found that trials which used SNOSE which were *not* opened by an independent third party tended to show a statistically significant treatment effect more often than trials which used more secure allocation methods.[40] Consequently, trials which simply describe the use of SNOSE without further elaboration about whether an independent third party was involved should be considered as having a high risk of bias when an important imbalance is identified; although chance imbalance cannot be ruled out, this more conservative approach seems reasonable (given the evidence).[40]

A case study has illustrated that forest plots of *baseline* data can be useful in checking for problems with baseline imbalance across trials (regardless of the causes of imbalance).[42] In this study an apparent treatment effect (weight loss) was found to be due to trial baseline imbalances in weight. However, in many reviews the included trials will be too heterogeneous to pool using meta-analysis, so studies are synthesised narratively. Here, the effect on review results of trials with important chance baseline imbalances needs particularly careful consideration.

A further advantage of actively identifying chance baseline imbalances lies in informing more specific review recommendations for designing future trials. For example, it may be evident that a future trial recruiting from a small population may benefit by using 'minimisation' randomisation methods[43] to reduce the possibility of an important chance imbalance occurring again.

Finally, the limitations of the approaches described in Paper 1[28] should be outlined. Firstly, the need to identify prognostic factors and effect modifiers means more work (and time) would be required of reviewers, compared with using the

unmodified tool. Consequently, the modifications may not be viable in all systematic reviews e.g. 'rapid reviews' where results are needed quickly. Another limitation is that the proposed modifications relate to trials which report unadjusted analyses; further considerations, beyond the scope of Paper 1,[28] are required for quality assessing trials which report adjusted analyses, such as the importance of relevant statistical expertise within a review team.

5.2 Improving the QUADAS-2 tool to allow assessment of comparative diagnostic test accuracy studies

Study types for evaluating diagnostic tests

In diagnostic studies the intervention being evaluated is a test, often a new test. New tests have been categorised as occupying one of three main positions in diagnostic pathways - replacement, triage, or add-on.[44] Most studies compare the accuracy of a single diagnostic test (called the index test) with a reference standard test. Reference standards are sometimes referred to as gold standards, but in practice they are rarely 100% accurate and are typically more invasive, expensive or time-consuming to implement than index tests.[45] Test accuracy outcomes are calculated from the numbers of "true positives" , "false positives", "false negatives" and "true negatives". Frequently reported outcomes include sensitivity, which is the proportion of people with disease who test positive, and specificity which is the proportion of people without disease who test negative.

Although most diagnostic test accuracy studies compare a single index test with a reference standard, where different test technologies exist in clinical practice it is preferable that studies of new tests compare the multiple index tests available. In these 'comparative' studies of test accuracy, patients typically receive an existing test, the new test, and a reference standard. Patients effectively act as their own controls, ensuring group comparability and minimising the number of patients required. Such studies are likely to be more relevant to clinical practice than studies of just a single index test. However, diagnostic accuracy studies do not tell us whether differences in accuracy result in clinically important effects on patient health outcomes. These effects may occur as a result of changes to further therapeutic or diagnostic interventions, based on test results. Randomised designs are often used when patient outcomes need evaluating. An RCT design may also be best where: tests are too invasive for both the current and new test to be done in the same patient; the tests interfere with each other; or the participation of patients in testing is assessed.[44]

Various RCT designs exist, based largely on where to randomise in the clinical or diagnostic pathway and on the types of outcomes being assessed.[44, 46] One option is randomisation to either a new test or an existing test (or to no test), with efficacy of subsequent treatment being evaluated; other types of outcome may also be assessed, such as the use of further diagnostic tests or use of therapeutic interventions. Another design option is for patients to receive a new test *and* an existing test followed by the therapeutic intervention (such as surgery, which may be risky and/or expensive) only if test results are concordant; patients with discordant test results are randomised to undergo the therapeutic intervention or not.[47]

Quality assessing diagnostic test studies

The QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies) and its previous version (QUADAS) is frequently used in systematic reviews to assess studies comparing single index tests with a reference standard. QUADAS-2 has some similarities to the aforementioned Cochrane risk of bias tool.[22] Firstly, its development arose from a need to address the limitations and variation seen across existing tools; a systematic review of tools for the quality assessment of diagnostic accuracy studies found that only 6 of 67 (9%) tools provided a definition of 'quality' and a specification of the aspects of quality the tool aimed to cover.[48] Secondly, QUADAS-2 is used to evaluate risk of bias across different methodological design domains. In QUADAS-2 there are four domains: patient selection, index test, reference standard, and flow and timing. Judgements are reported transparently (as high, low or unclear risk) guided by 'signalling questions' and the use of free text. Thirdly, QUADAS and QUADAS-2 have gone on to become frequently used and highly cited tools.

An important difference between the Cochrane risk of bias tool and QUADAS-2 is that the latter is not restricted to assessing bias (internal validity) since concerns about study applicability (external validity) are also evaluated. Nevertheless, QUADAS-2 was not designed to evaluate *comparative* diagnostic test accuracy studies. Although the developers originally intended to allow assessment to be made - in a separate domain - of studies comparing multiple index tests[49], poor inter-rater reliability and other problems were identified during piloting, so the domain was omitted from the final version of the tool.[22]

Paper 2[50] describes a modification of QUADAS-2 which was needed in a systematic review which included studies which compared two index tests with a reference standard. This review, of adjunctive colposcopy technologies,[51] was

commissioned by NICE so its results were to be used directly by decision makers faced with whether or not to recommend the new test technology. We therefore considered that a pragmatic approach to review methodology was essential to allow meaningful evaluations of the comparative studies, and so modified QUADAS-2, tailoring it to our review topic. We published details of our approach in Paper 2[50] to help guide other systematic reviewers undertaking reviews of comparative studies (i.e. studies with multiple index tests).

We modified QUADAS-2 in two main ways. First, we added review-specific questions to the index test and reference standard domains. For example, in the index test domain we asked whether operators had sufficient experience or training to administer each of the test technologies. We also added other questions, which did not relate to a particular domain. Second, for the index test domain, risk of bias and applicability judgements were made for *both* the index test and the comparator test, rather than just for the index test.[51]

Paper 2[50] describes all the modifications we made to QUADAS-2 for our systematic review. We then broadened the scope of Paper 2[50] by tabulating and discussing other issues that systematic reviewers may find relevant when quality assessing comparative studies (in addition to the questions we added in our review). The table included suggestions regarding which QUADAS-2 domain each question could be added to (see Table 1 in Paper 2[50]). An overarching theme was a consideration of whether aspects of study design and methodology favoured one test over another. Some issues related to internal validity, for example "Were the results of both tests verified using the same reference standard?" Some related to external validity, such as "Was the execution of both tests as they should be performed in clinical practice?"

Studies with RCT designs did not feature in our systematic review, which is one reason why Paper 2[50] only touched on diagnostic RCT quality assessment issues. The Cochrane RoB tool has been used to assess diagnostic RCTs which evaluate impact on patient outcomes.[52, 53] The downside to this approach is the omission of applicability issues. Given the very limited guidance on how to quality-assess diagnostic RCTs, a wider discussion is warranted.

Quality assessment issues in diagnostic RCTs

Although many consider that diagnostic RCTs are critical in the evaluation of novel tests in the presence of standard diagnostic tests,[54] they are rarely performed. This may be because randomisation is not mandatory in studies submitted to

support the regulatory approval of a test technology. It may also be because they are challenging to undertake due to reasons of sample size, cost, and complexity.[54] Complexity can arise because diagnostic RCTs evaluate management pathways, i.e. complex interventions. These have been described as 'test-treatment' strategies, comprising of four components: the test, diagnostic decision-making, management decision-making, and treatments. The reporting of these multi-staged interventions has been found to be very poor and inadequate for understanding trial results.[55] This poor reporting is likely to be a barrier to quality assessment since, to be informative, diagnostic RCTs should have a well-defined protocol that links test results to treatment strategies, e.g. a specific type of surgery for patients with positive test results and discharging patients with negative results.[56] Running diagnostic test trials without a protocol for translating the test results into clinical management decisions has been likened to trialling pharmaceuticals without pre-specifying the preferred dosage, optimum route of administration, the need for monitoring, or how to deal with adverse effects.[47] In addition to having a clear understanding of treatment strategies it is also important to analyse the processes which actually drive changes to health outcomes in each trial individually.[57]

Another issue with diagnostic RCT designs is that they are often considered to be statistically inefficient. In RCTs comparing tests, treatment effects can sometimes be diluted by the subgroup of patients whose diagnosis and treatment do not change.[57] One trial design is more statistically efficient than another if it yields more precise estimates when applied in similarly sized groups. Trial efficiency can be improved by moving the point of randomisation from the decision point of whether or not to test (or which test to give), to what to do with the test results, in terms of subsequent care and treatment.[47]

A review of the methodological quality of "test-treatment" RCTs found them to be particularly susceptible to attrition, lack of blinding and lack of power; they were also prone to having inadequately performed primary analyses.[58] The authors suggested that these issues may be a reflection of the methodological challenges that specifically affect test-treatment RCTs due to their multi-staged nature. However, in this review trials were assessed on internal validity issues, focussing on Cochrane risk of bias tool domains and trial conduct based on items from the CONSORT checklist for reporting randomised trials.[59] Quality assessment of a diagnostic RCT will be more challenging when patient outcomes *and* accuracy are being evaluated i.e. domains from both the Cochrane RoB tool and QUADAS-2 need to be considered.

Paper 2[50] was based on a single systematic review so the approaches suggested need further evaluation to identify any limitations. This should help to inform the next version of QUADAS-2. The issue of how to assess comparative studies is likely to arise more frequently in the future as more tests are adopted in clinical practice. Some systematic reviewers may even face the prospect of quality assessing studies with two or more comparator tests. In these situations assessments may become particularly convoluted, even with published guidance. The future of diagnostic RCT quality assessment seems even more complex. This is illustrated by an opinion piece on the design of diagnostic RCTs which ended by stating that "designing trials to evaluate the impact of tests on health requires creativity and care", and that "standard recipes will not suffice".[47] In systematic reviews similarly careful thought will be needed on how to assess trial quality. The need for guidance on how to quality-assess diagnostic RCTs may become much more urgent should the number of published trials increase dramatically. This could happen if regulatory approval requirements become more stringent.

6 Identifying areas of healthcare research where context-specific approaches to quality assessment will be beneficial

Papers 1[28] and 2[50] proposed approaches to improve established quality assessment tools, but even the best tools have limitations in their scope. In some areas of clinical research, studies will be affected by specific issues which are not covered by generic quality assessment tools. Awareness of such issues should prompt systematic reviewers to adopt a tailored approach to quality assessment, thinking beyond internal validity, to consider external validity and other factors.

Formal assessment of external validity is uncommon in systematic reviews, despite the availability of numerous tools and checklists.[20] The limited uptake of external validity tools could be due to the lack of empirical evidence to support and justify the inclusion of specific items[20, 60] and the time needed to use them. A methodological study on the usability and usefulness of applicability assessment tools was recently undertaken in "*an attempt to encourage the field to move beyond a recurring cycle of tool development without subsequent use*".[61] It found that none of eleven tools was ideal for assessing the applicability of a public health intervention, concluding that published tools may not be the best method for applicability assessment as they are likely to be either too long or incomplete, and may fail to address elements that matter for the topic of interest. However, these impracticalities, and the uncertainties about empirical evidence on what to assess, cannot conceal the fact that a study's external validity is important for both clinicians and decision makers.

The papers in this section identify example areas of clinical research where specific aspects of study quality are particularly important – aspects which are unlikely to be covered by widely-used generic quality assessment tools. Paper 3[62] investigates interventions given in emergency or urgent care settings; Paper 4[63] and Paper 5[64] both relate to studies comparing intervention delivery in different healthcare settings. Trial investigators in these areas of research may find that particularly careful deliberation of study design is needed when considering the trade-offs between achieving adequate internal validity, external validity and recruitment of a sufficient number of participants. Established quality assessment tools (such as the Cochrane risk of bias tool) will not cover all the implications of these sometimes difficult and nuanced decisions; implications which can be key not only in judging a trial's quality - and therefore its importance to clinical practice - but also in informing review recommendations for future research.

One such example, where the rationale for arriving at a difficult methodological decision was reported clearly, relates to a large quasi-randomised trial undertaken in an urgent care setting. The trial, which compared room air with 100% oxygen for resuscitating asphyxiated newborns, recruited 703 infants from 11 centres across six countries.[65] Treatments were allocated according to infant date of birth. In their methods section the authors stated:

> *"….after thorough consideration it was decided that formal randomization was not feasible in this study. Because resuscitation is a medical emergency requiring immediate treatment, we were concerned that a formal randomization (with, for instance, sealed envelopes) could have resulted in a delay in treatment. Such a delay also may have resulted in a reduced number of enrolled infants, especially the most depressed infants, possibly giving a non-representative sample."*

Quasi-randomised trials are judged as being at 'high risk' of selection bias using the Cochrane risk of bias tool (both the new and previous versions). However, in clinical situations like this, such a judgement seems somewhat over-simplistic, without providing further context.

6.1 Systematic reviews of interventions delivered in emergency or urgent care settings

The above example illustrates that in emergency or urgent care trials randomisation may sometimes be considered to result in clinically unacceptable treatment delays. Advances in technology may minimise delays to acceptable levels in some contemporary trials,[66] but systematic reviewers are more likely to encounter trials which used simpler methods where delays seem likely, such as allocating treatments using sequentially numbered, opaque sealed envelopes or randomising via a central telephone service. Nevertheless, methodologically sound randomisation methods can be used without causing treatment delays where interventions form discrete packs (which do not differ in appearance across trial treatments). Here, the randomisation sequence can be applied (in code, to minimise selection bias) onto treatment packs, with packs used sequentially.

However, in *some* trials which use true randomisation the recruitment of sufficient numbers of participants may be an issue because eligibility criteria have been narrowed to exclude patients perceived to be most prone to the effects of treatment delays. In addition to affecting accrual, these restrictions will limit the applicability of the trial population (and therefore the applicability of the trial results) to a

broader population. Moreover, in emergency setting trials where treatment delays due to randomisation *are* deemed to be clinically acceptable - such as the <30 second delay in the UK-REBOA trial of adults with confirmed or suspected life-threatening torso haemorrhage[66] - such delays will nevertheless not be truly reflective of clinical practice and hence might also reduce trial applicability.

Systematic reviewers evaluating trials performed in emergency or time-limited settings would therefore benefit from awareness of the variety of treatment allocation methods and their associated trade-off issues. Trials randomising individual patients will be internally valid but might consequently be quite small and have limited external validity. Trials using methods such as quasi-randomisation or cluster randomisation might achieve adequate trial recruitment and external validity but will be at risk of selection bias.[9, 67] Further consideration of the time restriction issue raised in the quasi-randomised trial of newborn resuscitation[65] prompted the following question: do investigators in time-limited settings have much opportunity for introducing selection bias, given the requirement for immediate treatment? The risk of bias tool requires users to think about the risk of selection bias but not whether the risk (of using the same methods) might vary by context (e.g. emergency versus non-emergency settings).

With these issues in mind, the study described in Paper 3[62] was undertaken to provide empirical data to inform risk of selection bias judgements and the applicability of emergency or urgent care trials. The study utilised the baseline assessment methods described in Paper 1.[28] The two main objectives were to obtain an estimate of the prevalence of important baseline imbalances when comparing true randomisation with quasi-randomisation and to assess indicators of external validity such as recruitment rates and the number of eligible patients who were not randomised. Given that small sample sizes were expected to be an issue, the likelihood of chance effects was also considered in Paper 3[62]. In this study, systematic reviews of emergency or urgent care interventions were eligible providing they included at least one quasi-randomised trial and one truly randomised trial (defined for the purposes of inclusion in this study as truly random sequence generation): seven reviews (27 trials) were included. The number of trials was limited primarily by the small number of quasi-randomised trials identified in the included reviews.

Important baseline imbalance was identified in four of the 16 trials which used true randomisation (25%) and in two of the 11 trials which used quasi-randomisation (18%). The study limitations included it being quite small and exploratory in

nature, and the possibility of baseline imbalances in unknown prognostic factors in the quasi-randomised trials. Nevertheless, as we did not find evidence that quasi-randomisation resulted in selection bias more often than true randomisation, our results suggested that high risk of bias judgements should not automatically be assumed when quasi-randomisation is used in urgent care trials. The restructured selection bias domain in version 2 of the Cochrane RoB tool uses baseline assessments primarily to identify the presence of bias, rather than its absence. However, given the evidence from Paper 3,[62] it seems reasonable to *consider* using 'low risk' judgments for emergency or urgent care trials with unclear or high risk methods, provided they show balance at baseline in all known effect modifiers and prognostic factors.

The most obvious and plausible mechanism to explain why bias could be less prevalent in emergency medicine trials is the lack of time prior to randomisation, making it difficult for investigators to fully assess prognosis. There is empirical evidence showing that biases may be less prevalent in trials of patients whose lives may be at risk.[63] Also, for all-cause mortality, a large meta-epidemiological study found no evidence of bias associated with inadequate or unclear allocation concealment (analysis of 209 trials), nor blinding (200 trials).[6] Although all-cause mortality may be frequently assessed in emergency care trials it is unclear how many of the trials[9, 68]in this study[6] were of interventions given in an emergency setting.

Of the four truly randomised trials that had an important baseline imbalance in Paper 3,[62] three described using adequate methods of allocation concealment. All three of these trials randomised 50 or fewer participants per arm, suggesting the imbalances were likely due to chance. These results show the value of considering whether trials have been affected by chance imbalances. Chance baseline differences might be expected to be more prevalent in small emergency care trials where delays in treatment must be minimal. This is because although the use of minimization or stratified randomization methods (used to reduce the possibility of imbalances) may sometimes be viable, they are more likely to be impractical - especially in older trials - due to insufficient time to obtain, record and input the relevant data needed.

Trial reporting limitations and clinical and methodological heterogeneity across trials within reviews, meant that limited comparative data were available for Paper 3's[62] remaining outcomes. The trial recruitment data indicated faster rates of estimated monthly patient accrual with quasi-randomisation (when compared with

true randomisation) in two reviews though no indication of differences in rates in two other reviews.

The issues raised in Paper 3[62] go beyond how best to assess trial quality in urgent care settings. Systematic reviewers should also consider the implications on the review's recommendations for future research. If the trade-offs and consequences of different approaches to allocating trial treatment are not identified then recommendations for research are likely to be uninformative, along the lines of "better quality, properly randomised trials are needed".

6.2 Systematic reviews of trials comparing the delivery of treatments in different healthcare settings

The importance of identifying specific issues of external validity is illustrated in Paper 4[63] - a systematic review evaluating chemotherapy delivery in different settings, such as hospital outpatient facilities, community facilities, or home. In that systematic review internal validity was assessed using the Cochrane risk of bias tool, modified as described in Paper 1.[28] From examining CONSORT diagrams and data on participant recruitment from the included studies it became evident that non-participation of eligible patients was an issue. Some patients declined to be randomised specifically because they had preferences for a particular healthcare setting. This results in 'enrichment' of the population, which can be exacerbated by not being able to blind randomised participants to their setting. Trial effect estimates may therefore be inflated driven by optimism in patients who received their setting of choice and disappointment in patients who did not. This may be particularly important for subjective outcomes, such as patient satisfaction and setting preference (often assessed in cross-over trials).

This enrichment issue affected trial quality by seriously limiting the applicability of the trial populations. This is illustrated by the OUTREACH parallel group trial, which compared chemotherapy delivery in three settings: hospital outpatient, GP surgery, and home.[69] Over a quarter of eligible patients declined participation for *setting-related* reasons, mostly because they preferred to have hospital outpatient chemotherapy - declining randomisation was the only sure way of achieving this, it being the standard of care. Further enrichment was likely to have occurred because the only way of (having a chance of) being treated at home or at a GP setting was to be randomised into the trial. Enrichment may therefore have occurred in two ways: patients who find hospitals reassuring declined participation and, conversely, hospital-averse patients were keen to be randomised. Interpretation of the OUTREACH results should therefore be qualified by an understanding that the

results relate specifically to a population enriched in patients who have pre-trial preferences for treatment in the community or at home. This greatly limits the applicability of its results to broader populations. This issue was common across many of the trials included in Paper 4.[63] It also had implications on sample size. All 10 included trials were small (range 10 to 97 participants). Six trials reported a target sample size. Three achieved or exceeded their small recruitment targets of 30 or fewer participants. The other three did not: in one, the target of 20 patients was not reached (for unclear reasons); one was terminated early because a large majority preferred the home setting after 52 of a targeted 160 participants had been randomised; and the OUTREACH trial was stopped after 2½ years by the independent data monitoring committee due to poor accrual.

Other external validity issues arose in Paper 4[63] – two of them related to outcomes. The first was that the quality of lifetools used did not appear to be sensitive enough to detect differences caused by the setting since they were designed to detect differences resulting from cancer therapies; any improvements in quality of life due to healthcare setting are likely to be evident in different domains of quality of life (to those assessed in the trials). The second issue related to preference as a trial outcome. In only one trial were participants asked about their *strength* of preference; around a third of patients said they would change their setting preference (from home to hospital, or vice versa) when told their preferred setting would involve an extra hour of waiting.[70] This suggests limited applicability for trial results which do not consider strength of preference – an outcome likely to be important for clinical commissioners.

One external validity issue related to the 'intervention'. This issue was the necessity to understand that trials of treatments delivered in different healthcare settings are evaluating complex interventions (i.e. it is not just the physical setting being evaluated). Consequently, trial results may only be applicable to the particular locations being studied because setting-related parameters are usually so location-specific. In Paper 4[63] these parameters might include travel distances, adequacy of parking facilities, outpatient staffing levels/waiting times and how fit for purpose the physical facilities were. Such factors can influence outcomes and may vary greatly across hospitals.

It has been argued that quality assessments should focus on internal validity since applicability is less relevant without internal validity.[17] Similarly, the explanation of item 21 of the CONSORT guidance on trial reporting states that:[59]

> "Internal validity is a prerequisite for external validity: the results of a flawed trial are invalid and the question of its external validity becomes irrelevant"

This is debatable to some extent – depending on how we define a 'flawed trial'. For example, trials where blinding is not possible may be at high risk of performance or detection biases but may nevertheless be the best *practicable* evidence possible. Moreover, the examples in Paper 4[63] raise the possibility of the converse sometimes being true: the results of a trial with adequate internal validity may have very limited relevance without an acceptable level of external validity. How useful are the results of trials which inform us that, in populations enriched in patients who prefer the home setting, patients prefer, and are more satisfied with, a home setting than with an outpatient setting?

The external validity issues identified in Paper 4[63] were invaluable not only for interpreting the meaning and value of trial results, but also for making recommendations for future research: exploration of the pre-trial preferences issue informed a discussion and recommendations of alternative trial designs, such as patient preference trials. This was particularly important in this systematic review because none of the 10 included RCTs used a preference trial design. It therefore appears that the difficult decisions regarding the aforementioned trade-offs between achieving adequate internal validity, external validity and sample size - which were evident in some of the trials included in Paper 3[62] - were not adequately considered in the trials included in Paper 4.[63] Trial investigators may have been too focussed on using conventional trial designs which were as internally valid as possible, but which ultimately had very limited applicability to the real populations of interest. In fairness to trial investigators, this approach may have been driven by necessity; guidance from funding agencies and ethics committees on the design and performance of RCTs has often focussed (at least historically) on internal validity, making little or no mention of external validity issues.[13]

How should reviewers assess external validity?

It is important to emphasise that trial external validity was not formally assessed in Paper 4.[63] The reasons for the limited use of external validity assessment tools in systematic reviews were discussed at the start of Section 6. Given these concerns and impracticalities, and given the abundance of possible issues which could affect study external validity,[13] a more realistic and practicable approach could be to

identify and then focus *only* on the review-specific issues which might influence effectiveness and implementation. For example, the U.S. Agency for Healthcare Research and Quality (AHRQ) methods guide recommends examination of a list covering a wide range of applicability items (based primarily on those described by Rothwell[13]) followed by the selection of a small subset of important items, preferably those which have been associated with differences in treatment outcomes.[71] Advice from clinical experts and stakeholders can help to identify the most relevant issues. Reviewers can then systematically extract relevant information and describe the impact of applicability on the interpretation of individual studies.

Evaluation of trial population characteristics is the aspect of external validity which is perhaps most frequently considered in systematic reviews. It is here that added benefit can be derived from the information acquired as a result of the methods proposed in Paper 1.[28] The important effect modifiers and prognostic factors identified prior to risk of bias assessments can also be used to evaluate the applicability of trial populations. Rather than considering differences between *groups* within a trial (as in risk of bias assessments), here we are interested in whether important characteristics differ between *populations* across trials or between trial populations and the population expected to be seen in clinical practice. This approach would minimise the possibility of reviewers failing to identify population variation across studies which affects outcomes.

The implications of the patient preference issue encountered in Paper 4[63] led to a study to investigate the impact of pre-trial preferences on participation in *any* healthcare setting trial - Paper 5.[64] This exploratory methodological review also sought to identify any other methodological issues which might be encountered in setting trials. The study found evidence that accrual in trials of healthcare settings is often affected by patient preferences. This may result in enriched populations being recruited which can serious limit trial applicability. In light of these findings the proportion and reasons for patients declining randomisation should be an important part of study quality assessments when healthcare setting trials are systematically reviewed. Results from trials which do not report such details should be viewed cautiously. Where preference itself is an outcome (as may be seen in cross-over trials) this lack of reporting might be viewed as a type of reporting bias; some investigators might opt not to report on pre-randomisation data if they suggest that the recruited population is skewed in terms of pre-trial setting preferences.

Trials identified in Paper 5[64] also provided examples which:

i) Suggest that accrual may be difficult in setting trials if usual care settings are satisfactory i.e. there needs to be a perceived demand for alternatives. This will be especially important to consider in multi-site trials where heterogeneity of standard of care is likely, and,

ii) Reinforced the earlier finding of the need for reviewers to understand that 'settings' form part of multi-component, complex interventions. Attempts to perform trials which aim to separate out a 'setting effect' from interacting organisational and care parameters are likely to encounter problems.

Paper 5[64] would therefore be very useful for both systematic reviewers and trialists intending to study healthcare settings. In systematic reviews it should prompt careful thought of study design eligibility criteria - researchers may otherwise be unaware of the existence of preference trial designs. Similarly, it would be beneficial in providing insight (and references) for making recommendations for future research. Primarily though it should focus study quality assessments on the most import aspects of external validity, such as enrichment due to patient preference. Paper 5's[64] findings may also have broader value, being of interest to those undertaking systematic reviews of *any* interventions where pre-trial patient preferences are anticipated.[72]

The information that Paper 5[64] provides to systematic reviewers on the design and advantages of patient preference trials returns us to an underlying theme of this thesis - that approaches to quality assessment continue to evolve and may need to be adapted. A question that might inevitably arise in some reviews of setting trials is: *How should I assess the quality of a preference trial?*

7 Conclusions

The ideas presented in this thesis for enhancing established quality assessment tools have already had an impact. The proposal to assess trial baseline characteristics for important imbalances[28] has been incorporated into version 2 of the Cochrane RoB tool.[38] The first author of Paper 3[62] has been invited by the QUADAS-2 developers to provide input to help inform an updated version, covering comparative studies. The papers on topic-specific approaches should be invaluable in helping systematic reviewers identify and focus on important aspects of study quality which might otherwise be missed using standard tools. They particularly highlight the importance of reviewers being aware of the range of issues which might affect a trial's external validity. A development from considering the thesis papers collectively is the value of making use of knowledge of important baseline characteristics - identified as part of risk of bias assessments using RoB version 2 - to enable a focused assessment of trial population applicability.

Some systematic reviewers will assess only risk of bias when quality assessing studies, but it is clear that a broader assessment is needed if important issues are not to be missed. The success of the Cochrane RoB tool - spearheaded by the Cochrane Collaboration and guidance in the PRISMA statement[73] - has arguably come at a price of focusing too much reviewer attention on issues of internal validity, at the expense of external validity. This thesis presents examples of problems encountered in trials which needed to - but did not - find the correct balance between reducing bias and recruiting an adequately sized and representative cohort. They highlight the importance of external validity and chance effects when considering study quality. The content and structure of QUADAS-2 is more balanced than the Cochrane risk of bias tool as it ensures that reviewers consider risk of bias *and* applicability issues. Even here important issues might still be missed e.g. chance effects or the use of inappropriate statistical methods.

Reviewers should therefore not rely solely on 'off-the-shelf' tools, but be vigilant and open-minded about issues which emerge during the course of a review: issues important in *their* particular review, but which do not arise in most reviews; issues which could be missed, primarily because they may not be on the quality assessment 'radar', or because they may not have been encountered before by the reviewer (e.g. publication retractions)

Systematic reviews should be key in informing the relevance and design of proposed new trials.[74] Formal frameworks exist to identify research gaps from systematic reviews[75] but recommendations are often limited, with some reviews simply resorting to brief truisms along the lines of "high quality studies are needed". What *is* needed are more specific details of what issues need to be addressed, together with suggestions for the most appropriate and viable study designs. The former should become evident from identifying key study quality issues and the latter should be researched by the reviewer when writing the review discussion. This approach should optimise the resulting research recommendations, which should be valuable for both commissioners of new trials and for the investigators who ultimately design them. This thesis illustrates that undertaking enhanced quality assessments can lead to more informative review recommendations for research. Examples include: consideration of the trade-offs and consequences of different approaches to allocating treatments in trials where treatment delays must be very brief; the use of patient preference trial designs where intervention settings are being studied; and the use of minimisation or stratification methods where important chance imbalances may be likely. Moreover, review recommendations need not be restricted to future trials e.g. research on effect modification might be recommended.

Future research with respect to the thesis papers is needed. Firstly, to evaluate the impact of using baseline assessments to inform RoB judgements by, for example, considering how many 'unclear' risk judgements are resolved when reviews are updated, and whether there are disadvantages to this new approach. Further research on the risk of selection bias in emergency setting trials would benefit from including a larger cohort of trials. This could be achieved by comparing effect estimates in trials with 'low risk' of bias from allocation concealment with trials with 'unclear risk' or 'high risk' of bias, using similar methods to those in Wood et al's meta-epidemiological study of the effect of trial biases.[6]

Research is also warranted on how external validity is assessed in systematic reviews. A survey of systematic reviewers could inform on current approaches to assessments, awareness of tools/issues, and opinions on whether a new tool is needed. In the meantime, use of the aforementioned AHRQ methods guide, seems a useful and practicable approach. Reviewer time may be most efficiently used by only assessing external validity in those studies which are as internally valid as possible, since little is likely to be gained from considering the external validity of studies with *avoidable* biases. QUADAS-2 would be a good tool for piloting this idea, since it assesses both risk of bias and applicability.

8 References

1. Boutron I, Ravaud P. Classification systems to improve assessment of risk of bias. *J Clin Epidemiol* 2012;**65**:236-8.

2. Young JM, Solomon MJ. How to critically appraise an article. *Nat Clin Pract Gastroenterol Hepatol* 2009;**6**:82-91.

3. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;**64**:383-94.

4. Altman DG. The scandal of poor medical research. *Bmj* 1994;**308**:283-4.

5. Glasziou P, Djulbegovic B, Burls A. Are systematic reviews more cost-effective than randomised trials? *Lancet* 2006;**367**:2057-8.

6. Horton R. Health research in the UK: the price of success. *Lancet* 2006;**368**:93-7.

7. Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. *Lancet* 2010;**376**:20-1.

8. Glasziou P, Chalmers I. Research waste is still a scandal-an essay by Paul Glasziou and Iain Chalmers. *Bmj* 2018;**363**:k4645.

9. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336**:601-5.

10. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 1995;**16**:62-73.

11. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *Bmj* 2001;**323**:42-6.

12. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

13. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005;**365**:82-93.

14. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1-12.

15. *PEDro Scale*. Available from: https://www.pedro.org.au/english/downloads/pedro-scale/ [accessed 07/01/2019]

16. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;**282**:1054-60.

17. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

18. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* 2015;**16**:495.

19. Rothwell PM. Commentary: External validity of results of randomized trials: disentangling a complex concept. *Int J Epidemiol* 2010;**39**:94-6.

20. Burchett H, Umoquit M, Dobrow M. How do we know when research from one setting can be useful in another? A review of external validity, applicability and transferability frameworks. *J Health Serv Res Policy* 2011;**16**:238-44.

21. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, et al. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. *PLoS Med* 2016;**13**:e1002028.

22. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529-36.

23. *CONSORT. Transparent reporting of trials.* The CONSORT Group; Available from: http://www.consort-statement.org/ [accessed 07/01/2019]

24. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016;**6**:e012799.

25. Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev* 2012;**11**:MR000030.

26. Korevaar DA, van Enst WA, Spijker R, Bossuyt PMM, Hooft L. Reporting quality of diagnostic accuracy studies: a systematic review and meta-analysis of investigations on adherence to STARD. *Evid Based Med* 2014;**19**:47-54.

27. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud* 2013;**50**:587-92.

28. Corbett MS, Higgins JPT, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Res Synth Methods* 2014;**5**:79-85.

29. Corbett MS, Rice SJC, Madurasinghe V, Slack R, Fayter DA, Harden M, et al. Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis. *Osteoarthritis Cartilage* 2013;**21**:1290-8.

30. Sormani MP. Prognostic factors versus markers of response to treatment versus surrogate endpoints: Three different concepts. *Mult Scler* 2017;**23**:378-81.

31. Hulshof TA, Zuidema SU, van Meer PJK, Gispen-de Wied CC, Luijendijk HJ. Baseline imbalances and clinical outcomes of atypical antipsychotics in dementia: A meta-epidemiological study of randomized trials. *Int J Methods Psychiatr Res* 2019;**28**:e1757.

32. Page MJ, Higgins JPT, Clayton G, Sterne JAC, Hrobjartsson A, Savovic J. Empirical Evidence of Study Design Biases in Randomized Trials: Systematic Review of Meta-Epidemiological Studies. *PLoS One* 2016;**11**:e0159267.

33. Senn S. Seven myths of randomisation in clinical trials. *Stat Med* 2013;**32**:1439-50.

34. Olsen MF, Bjerre E, Hansen MD, Tendal B, Hilden J, Hrobjartsson A. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. *J Clin Epidemiol* 2018;**101**:87-106.e2. A

35. Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M, et al. Certolizumab pegol and secukinumab for treating active psoriatic arthritis

following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation. *Health Technol Assess* 2017;**21**:1-326.

36. Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. *RMD Open* 2015;**1**:e000017.

37. Corbett M, Higgins J, Woolacott N. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. In: *Better Knowledge for Better Health Abstracts of the 21st Cochrane Colloquium*; 2013 19-23 Sep; Québec City, Canada. John Wiley & Sons; 2013.

38. *Revised Cochrane risk of bias tool for randomized trials (RoB 2)*. 2017. Available from: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool [accessed 11th December 2018]

39. Clark L, Fairhurst C, Torgerson DJ. Allocation concealment in randomised controlled trials: are we getting better? *BMJ* 2016;**355**:i5663.

40. Hewitt C, Hahn S, Torgerson DJ, Watson J, Bland JM. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. *BMJ* 2005;**330**:1057-8.

41. Davey J, Turner RM, Clarke MJ, Higgins JPT. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. *BMC Med Res Methodol* 2011;**11**:160.

42. Trowman R, Dumville JC, Torgerson DJ, Cranny G. The impact of trial baseline imbalances should be considered in systematic reviews: a methodological case study. *J Clin Epidemiol* 2007;**60**:1229-33.

43. Treasure T, MacRae KD. Minimisation: the platinum standard for trials?. Randomisation doesn't guarantee similarity of groups; minimisation does. *Bmj* 1998;**317**:362-3.

44. Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. *BMJ* 2006;**332**:1089-92.

45. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination, University of York; 2009. Available from: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf

46. Lijmer JG, Bossuyt PMM. Various randomized designs can be used to evaluate medical tests. *J Clin Epidemiol* 2009;**62**:364-73.

47. Bossuyt PM, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. *Lancet* 2000;**356**:1844-7.

48. Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J. A systematic review finds that diagnostic reviews fail to incorporate quality despite available tools. *J Clin Epidemiol* 2005;**58**:1-12.

49. Whiting P, Rutjes A, Westwood M, Mallett S, Leeflang M, Reitsma H, et al. *Updating QUADAS: evidence to inform the development of QUADAS-2*. 2010. Available from: www.bris.ac.uk/quadas/resources/quadas2reportv4.pdf [accessed 11th May 2018]

50. Wade R, Corbett M, Eastwood A. Quality assessment of comparative diagnostic accuracy studies: our experience using a modified version of the QUADAS-2 tool. *Res Synth Methods* 2013;**4**:280-6.

51. Wade R, Spackman E, Corbett M, Walker S, Light K, Naik R, et al. Adjunctive colposcopy technologies for examination of the uterine cervix-DySIS, LuViva

Advanced Cervical Scan and Niris Imaging System: a systematic review and economic evaluation. *Health Technol Assess* 2013;**17**:1-240, v-vi.

52. Westwood M, Ramaekers B, Whiting P, Tomini F, Joore M, Armstrong N, et al. Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2015;**19**:v-xxv, 1-236.

53. Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2015;**19**:1-228, v-vi.

54. Rodger M, Ramsay T, Fergusson D. Diagnostic randomized controlled trials: the final frontier. *Trials* 2012;**13**:137.

55. Ferrante di Ruffano L, Dinnes J, Taylor-Phillips S, Davenport C, Hyde C, Deeks JJ. Research waste in diagnostic trials: a methods review evaluating the reporting of test-treatment interventions. *BMC Med Res Methodol* 2017;**17**:32.

56. Bossuyt PMM, Reitsma JB, Linnet K, Moons KGM. Beyond diagnostic accuracy: the clinical utility of diagnostic tests. *Clin Chem* 2012;**58**:1636-43.

57. Ferrante di Ruffano L, Deeks JJ. Test-treatment RCTs are sheep in wolves' clothing (Letter commenting on: J Clin Epidemiol. 2014;67:612-21). *J Clin Epidemiol* 2016;**69**:266-7.

58. Ferrante di Ruffano L, Dinnes J, Sitch AJ, Hyde C, Deeks JJ. Test-treatment RCTs are susceptible to bias: a review of the methodological quality of randomized trials that evaluate diagnostic tests. *BMC Med Res Methodol* 2017;**17**:35.

59. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010;**63**:e1-37.

60. Dyrvig A-K, Kidholm K, Gerke O, Vondeling H. Checklists for external validity: a systematic review. *J Eval Clin Pract* 2014;**20**:857-64.

61. Burchett HED, Blanchard L, Kneale D, Thomas J. Assessing the applicability of public health intervention evaluations from one setting to another: a methodological study of the usability and usefulness of assessment tools and frameworks. *Health Res Policy Syst* 2018;**16**:88.

62. Corbett MS, Moe-Byrne T, Oddie S, McGuire W. Randomization methods in emergency setting trials: a descriptive review. *Res Synth Methods* 2016;**7**:46-54.

63. Corbett M, Heirs M, Rose M, Smith A, Stirk L, Richardson G, et al. The delivery of chemotherapy at home: an evidence synthesis. *Health Services and Delivery Research* 2015;**3**:1-182.

64. Corbett MS, Watson J, Eastwood A. Randomised trials comparing different healthcare settings: an exploratory review of the impact of pre-trial preferences on participation, and discussion of other methodological challenges. *BMC Health Serv Res* 2016;**16**:589.

65. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics* 1998;**102**:e1.

66. *Protocol UK-REBOA trial*. Available from: https://w3.abdn.ac.uk/hsru/REBOA/Public/download.aspx?ID=142 [accessed 29th November 2018].

67. Hahn S, Puffer S, Torgerson DJ, Watson J. Methodological bias in cluster randomised trials. *BMC Med Res Methodol* 2005;**5**:10.

68. Anthon CT, Granholm A, Perner A, Laake JH, Moller MH. No firm evidence that lack of blinding affects estimates of mortality in randomized clinical trials of intensive care interventions: a systematic review and meta-analysis. *J Clin Epidemiol* 2018;**100**:71-81.

69. Corrie PG, Moody AM, Armstrong G, Nolasco S, Lao-Sirieix SH, Bavister L, et al. Is community treatment best? a randomised trial comparing delivery of cancer treatment in the hospital, home and GP surgery. *Br J Cancer* 2013;**109**:1549-55.

70. King MT, Hall J, Caleo S, Gurney HP, Harnett PR. Home or hospital? An evaluation of the costs, preferences, and outcomes of domiciliary chemotherapy. *Int J Health Serv* 2000;**30**:557-79.

71. U. S. Department of Health & Human Services Agency for Healthcare Research and Quality. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Assessing the Applicability of Studies When Comparing Medical Interventions*. 2010. Available from: https://effectivehealthcare.ahrq.gov/topics/methods-guidance-applicability/methods [accessed 30th November 2018].

72. King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, et al. Impact of participant and physician intervention preferences on randomized trials: a systematic review. *Jama* 2005;**293**:1089-99.

73. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.

74. Jones AP, Conroy E, Williamson PR, Clarke M, Gamble C. The use of systematic reviews in the planning, design and conduct of randomised trials: a retrospective cohort of NIHR HTA funded trials. *BMC Med Res Methodol* 2013;**13**:50.

75. Robinson KA, Saldanha IJ, McKoy NA. Development of a framework to identify research gaps from systematic reviews. *J Clin Epidemiol* 2011;**64**:1325-30.

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Research Synthesis Methods

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Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool

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A key component of the Cochrane Collaboration's risk of bias tool for critically evaluating randomised trials is the consideration of whether baseline characteristics of the treatment groups being compared are systematically different. Considered under the domain of 'selection bias', this is currently evaluated by looking at the methods of randomisation and specifically at the generation of the randomised allocation sequence and the concealment of this sequence during the process of randomisation. Assessment of the actual similarity of baseline variables across groups in demographic and clinical characteristics is seldom performed. Even when performed, the link with selection bias is sometimes not considered.

Methods of randomisation and allocation concealment are often poorly reported in published trials, yet baseline data tables are presented in a large majority of trial reports. In this article, we propose that assessment of trial baseline data should form a key and prominent part of selection bias judgements when using the risk of bias tool. We outline the possible benefits from using this approach, including reduced uncertainty in systematic review conclusions, reduced risk of chance findings being ascribed to treatment effects and better use of available evidence by a more considered approach to evaluating studies using imperfect randomisation and allocation methods. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: risk of bias; systematic reviews; baseline imbalance; randomised trials; Cochrane Collaboration

1. Background

The Cochrane risk of bias tool is widely used in systematic reviews of the effects of interventions for critically assessing randomised trials in a detailed and transparent way (Higgins *et al*., 2011). The tool assesses the risk that bias resulting from limitations in design and conduct of the trial may lead to overestimation or underestimation of treatment effects. Bias is defined by the tool's authors as 'systematic error or deviation from the truth in results or inferences'. An assessment of the risk of bias constitutes an important part of the systematic review process, because it indicates whether the findings from a trial are likely to be reliable.

A key component of the current version of the risk of bias tool is the assessment of the extent to which intervention groups are similar at the start of the trial. The Cochrane Collaboration has traditionally used the term 'selection bias' for bias relating to non-comparability of groups, although the term is used in observational epidemiology for biases in selection of participants into the study (baseline differences would usually be considered to be confounding). Assessment of selection bias due to non-comparability of groups is currently achieved through consideration of the methods used to generate the randomisation sequence and to conceal this sequence during the randomisation process. Details of these methods from trial reports are summarised and used to inform judgements about the risk of selection bias arising separately from sequence generation and sequence concealment.

A different source of information that is relevant to the risk of selection bias is the actual similarity in baseline characteristics of participants allocated to the different treatment groups. Assessment of baseline imbalances in demographic and clinical characteristics–particularly those known to be prognostically important–can indicate whether randomisation is likely to have been performed appropriately (or even performed at all), and whether the use of randomisation successfully achieved comparability across the randomised groups. Use of poor methods

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may introduce bias according to the definition in the opening paragraph. However, differences despite sound randomisation methods arise because of chance. Nevertheless, it can be important to identify chance differences in systematic reviews because most meta-analyses include very small numbers of studies; (Davey *et al*., 2011) in these analyses, it should not be assumed that any baseline differences will balance out. Systematic reviewers frequently have to draw conclusions from one or two small studies that display notable differences in baseline characteristics across treatment groups.

Ideally, all published randomised trials would report methods in detail according to CONSORT recommendations (CONSORT, 2012). Recently-published evidence from a study comparing pre-CONSORT reporting (in 1995) with post-CONSORT reporting (in 1997 and 2002) has observed only a slow improvement in reporting of randomisation methods. Six years after CONSORT was published, most trials did not adequately explain their randomisation methods, even in high-impact journals that recommend the use of CONSORT: only 13 out of 33 (39%) Lancet papers, and 8 out of 44 (18%) JAMA papers adequately explained methods of randomisation (Clement and Buckley, 2011). In contrast, trial baseline data tables–also an item in the CONSORT statement–were very widely reported. Of 114 randomised trials reported in four high-impact journals in the first half of 2007, 110 (96.5%) presented such a table (Austin *et al*., 2010). In the absence of detailed randomisation methods, these baseline data tables might provide an important source of information for assessing whether the methods used were successful in achieving comparability of groups.

2. The Cochrane risk of bias tool

The first version of the risk of bias tool was described in 2008 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2008) with an updated version published in 2011 (Higgins *et al*., 2011; Higgins and Green, 2011). In the current (2011) version, the tool considers seven items in six domains of bias, with selection bias being the sole domain with two items (Table 1). Each item is addressed by a narrative description of that aspect of trial conduct and a judgement about the risk of bias that might arise as a consequence ('high risk', 'low risk' or 'unclear risk' of bias). The guidance for using the tool states that the presence of baseline imbalance could be assessed as part of the 'Other bias' domain. However, the guidance argues that imbalance arises primarily because of inadequate methods of randomisation (generation and/or concealment of the sequence) or through differential exclusions of participants (yielding incomplete outcome data) and so should be addressed via these standard items in the tool. Consequently, baseline imbalance is seldom included in risk of bias assessments. Of 1399 Cochrane reviews in one particular sample with completed risk of bias tables, only 121 (8.6%) assessed baseline imbalance as part of the other bias domain (personal communication with Jelena Savovic, University of Bristol, 29th November 2012). We suspect that in many of these instances, the link with selection bias would not have been considered explicitly.

3. A proposal to consider baseline imbalance routinely

Failure to assess baseline imbalance in randomised trials included in systematic reviews may lead to review conclusions being either unnecessarily conservative or over-optimistic. For example, if randomisation methods are unclear, then the risk of selection bias in the included studies will be unclear, with consequent reticence to draw firm conclusions from the review. But if baseline data demonstrate that all important prognostic factors were balanced across arms, then that reticence may be misplaced. Alternatively, randomisation methods may appear robust, but important group baseline imbalance not noticed, leading to unwarranted confidence in the findings of the study and hence in the broader findings of the review; selection bias is low as formally defined, but chance differences may need to be considered.

We propose that baseline imbalance should be considered routinely in assessments of the risk of selection bias. To inform this, important prognostic factors and the magnitude of the difference between groups that would be sufficient to raise concern should be pre-specified in a review protocol.

A risk of bias judgement using the Cochrane tool should relate to the results of the study as they are included in the review and in meta-analyses. This result may arise from an unadjusted analysis or an analysis that adjusts for baseline variables (possibly including a baseline measure of the outcome variable). In this paper, we focus only on unadjusted analyses; further considerations are required if the trial authors present analyses that adjust for baseline imbalances.

Table 2 presents our framework and outlines the potential implications of considering baseline imbalances alongside the randomisation methods. Judgements highlighted in grey indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using the tool as currently described. In the sections that follow, we elaborate on these situations, drawing on examples from reviews recently conducted by the Centre for Reviews and Dissemination. For the remaining situations, adding baseline assessment would not change the judgements but may allow them to be made with added confidence.

Table 1. The Cochrane risk of bias tool (reproduced from Higgins *et al*. (2011)).

Bias domain	Support for judgement	Review authors' judgement (Assess as low, unclear or high risk of bias)
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biassed allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of or during enrolment.	Selection bias (biassed allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind trial participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors and what was found.	Reporting bias due to selective outcome reporting
Other bias		
[Anything else, ideally pre-specified]	State any important concerns about bias not addressed in the other domains in the tool.	Bias due to problems not covered elsewhere in the table

Table 2. Selection bias decisions for trials reporting unadjusted analyses–comparison of results obtained using method details alone with results using method details and trial baseline information.

Reported randomisation and allocation concealment methods	Risk of bias judgement using methods reporting	Information gained from study characteristics data	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	Unclear risk[i]
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables*	Low risk
		No Baseline details	Unclear risk
Sequence is not truly random, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables*	Unclear risk
		No baseline details	High risk

*Details for the remaining important prognostic variables not reported, [i]Imbalance identified which appears likely to be due to chance.

4. Resolution of unclear risk of selection bias

Judgements of unclear risk of selection bias are common due to poor reporting of trial methodology. In one study of the Cochrane risk of bias tool, unclear risk assessments were recorded for sequence generation in 107 of 163 trials (66%) compared with 52 low risk assessments (32%) and 4 high risk assessments (2%); and results for allocation concealment were almost identical (Hartling *et al.*, 2009). Furthermore, a recent study of published reports of 429 trials of cancer patients highlighted that they do not always reflect the actual high quality of methods found in the trial protocols: 95% of the trials reported adequate methods for allocation concealment in their protocols compared with only 24% in the final published papers (Mhaskar *et al.*, 2012). For sequence generation, the corresponding proportions were 39% and 23%, respectively. Similar results were found in a study of 95 cancer trials, where additional information collected for individual patient data meta-analyses was used to inform judgements (Vale *et al.*, 2013).

We propose the use of data on baseline characteristics–which are normally tabulated in trial reports–to convert unclear risk judgements to low risk judgements when there is evidence of baseline comparability on all important potential prognostic variables. Alternatively, when important imbalance is identified amidst uncertainty about the randomisation methods, then we suggest a judgement of high risk of selection bias be made. We recognise that such imbalances could either be due to inappropriate randomisation methods or due to the play of chance. Without information to distinguish the two, we propose to err on the side of caution.

Examples of both of these types of resolution of an unclear risk judgement can be found in trials included in a systematic review of physical treatments for pain due to knee osteoarthritis, a condition for which baseline pain (Tubach *et al.*, 2005) and weight/body mass index (BMI) (National Collaborating Centre for Chronic Conditions, 2008) are relevant prognostic indicators of outcome. Recent research suggests that symptom duration and gender should also be considered as important prognostic demographics (Chapple, 2011). All these factors appear particularly relevant in this context, because all would, or could, be known by an investigator involved in the randomisation process.

For one trial, the randomisation method was unclear (the study appeared to use block randomisation, but no further details were reported) (Kuptniratsaikul *et al.*, 2002). Nevertheless, among the 392 randomised participants, the two treatment groups were similar at baseline for pain scores (a 0.3 difference, on a 0–10 visual analogue scale) and also very similar for duration of pain, BMI and gender; thus lessening the risk that bias had affected the study results but not eliminating it as a possibility. Thus, the unclear risk could reasonably be amended to low risk. A second trial compared two forms of exercise with a control group in 79 patients (Lund *et al.*, 2008). Although treatment allocation was concealed using opaque envelopes, the method of sequence generation was not described (only

the term 'randomised' was used), so a definitive judgement could not be reached about risk of selection bias on the basis of the reporting alone. There were noticeable baseline differences between groups in this three-armed trial. A 14.3 point difference in pain at rest and an 11.3 point difference for pain when walking (on a 0–100 visual analogue scale) were evident between the aquatic exercise and standard care groups. Furthermore, the baseline mean weights of participants were 81.1 kg (aquatic exercise), 67.6 kg (land-based exercise) and 77.3 kg (standard care). These differences are substantial enough to lead to important concerns about the validity of analyses based on post-treatment measures, so whilst one cannot for certain attribute this to a systematic error, the impact of the study on the review is not easily distinguishable from that of a study that used inadequate randomisation methods, and we judged the study to be at high risk of bias.

5. Re-classification of low risk of selection bias

Baseline imbalance can occur by chance even when randomisation methods are adequate (and hence judged to be at low risk of bias). Larger absolute magnitudes of imbalance are more likely in small trials, and less likely in large trials, especially if they use stratified randomisation or minimisation techniques, designed to reduce imbalances in specific characteristics. If several studies are included in a meta-analysis, chance differences should balance out across studies. However, in practice, this may not happen, or there may be too few studies included to allow this. Even when a large number of studies are included in a review, subgroup or sensitivity analyses may include few studies, and results from studies with important imbalances may bias these results.

Routine examination for baseline imbalance may identify situations in which 'unlucky' randomisation should lead to important concern about the validity of the findings. We acknowledge that statistical testing for differences in baseline characteristics is particularly inappropriate when the randomisation methods were sound (Austin *et al*., 2010). However, large magnitudes of baseline imbalance on important prognostic variables frequently give rise to concern. We propose that such concerns about baseline imbalance warrant a downgrading of a low risk of selection bias to an unclear risk judgement, despite the apparently sound methodology for the randomisation.

In a review of the drug tafamidis for treating transthyretin familial polyneuropathy (a rare neurodegenerative disease), an international multi-centre study by Coelho *et al*. had apparently sound randomisation methods: the process was centralised, with an interactive voice response system producing treatment allocations and study identification numbers (Coelho *et al*., 2012). The study randomised 128 patients and a co-primary outcome of interest was the Neuropathy Impairment Score for the Lower Limb (NIS-LL, a measure of disease progression, with higher scores reflecting worsening outcomes) at 18 months. The tafamidis group had lower baseline NIS-LL scores than the placebo group (median difference 2 points), yet a longer disease duration prior to randomisation (median difference: 7 months). Taken together, these suggest a faster rate of disease progression in the placebo group, leading to concerns about the baseline comparability of participants. Although baseline NIS-LL was found to be a significant covariate predictor of NIS-LL response, baseline NIS-LL score was not incorporated into the analysis as a covariate. For this example, a re-classification from low risk to unclear risk therefore appears warranted.

In order to differentiate an unclear risk judgement that appears to arise from a chance imbalance from an unclear risk judgement that arises from genuine uncertainty in the randomisation methods, the free-text field within the tool providing support to the judgement should be used (Table 2). Identification of the chance imbalance in the Coelho *et al*. trial was particularly important for the transthyretin familial polyneuropathy review, because it was the only randomised trial included in the review. The usefulness of the trial's findings was questionable. Similar situations will arise in reviews that synthesise studies narratively. Conversely, in reviews with many trials in which chance imbalances are identified, a meta-analysis result may be interpreted as being robust.

For trials not reporting one or more of the pre-specified important prognostic baseline variables, an overall judgement of low risk appears reasonable when the randomisation methods are robust, despite the incomplete baseline data.

6. Re-classification of high risk of bias

Trials assessed as at high risk of bias on the randomisation methods alone will have used methods that make them susceptible to bias, but this potential might not be translated into actual non-comparability of groups at baseline. Use of suboptimal randomisation methods may be due to clinical practicalities or resource limitations. For instance, use of a patient's hospital number might be used when treatment needs to start immediately, in which case the use of more robust, time-consuming methods might not be feasible. Suboptimal methods do not necessarily imply that the allocations were manipulated. Examination of a study characteristics table may be able to clarify whether such bias is present. In some trials, adequate similarity across baseline will be achieved. The results of such studies could therefore be considered as being at a low risk of bias. This is not to say that the study is entirely free of bias (hence the classification of low risk rather than 'no risk'), but we argue that this is a

reasonable judgement to reach based on the totality of information relevant to selection bias. The judgement of low risk of bias avoids underestimating the reliability of potentially valuable results. We note that this argument leads to concerns about the appropriateness of automatically excluding quasi-randomised trial evidence from systematic reviews without a more detailed evaluation of whether their results are likely to be biassed. This issue has been raised in a recent blog post (Herbison, 2012).

In a trial of people with osteoarthritis, Adedoyin *et al*. used alternation to assign 30 patients to two treatment groups (Adedoyin *et al*., 2002). Nevertheless, the groups were similar in baseline pain on a 10-point scale (8.1 versus 7.6) and in BMI (27.7 versus 28.8 kg/m^2), suggesting that the process did not lead to serious imbalance between the two groups. No details were reported to allow group comparison for gender, or for symptom duration, so an unclear risk of bias judgement might be considered here. Had these missing data been reported, and shown balance, a high risk to low risk conversion would have been a reasonable judgement.

7. Discussion

Assessment of risk of bias of a randomised trial involves evaluation of the extent to which the groups are free of systematic differences in important baseline characteristics (often referred to as selection bias). The explicit assessment of baseline similarities should routinely be considered alongside an assessment of selection bias. We therefore propose in this paper that assessment for group baseline imbalances should form a key and prominent part of the Cochrane risk of bias tool. The results of such assessments should be documented as part of the selection bias domain. By considering not only what trial investigators aimed to achieve by their methods, but also what they actually *did* achieve in practice, we hope to enable a more comprehensive and accurate assessment. Although we have cited examples from clinical trials to illustrate our proposal, it is also applicable to other areas of research where randomised trials are performed. Because important chance imbalances (as well as those caused by systematic bias) are often of interest to systematic reviews, we have proposed that, where possible, they should also be identified during selection bias evaluations. Chance imbalances might also affect judgements around the risk of attrition bias: the specific identification of potentially important imbalances in withdrawals and drop-outs, which appear likely to be due to chance, might improve the limited inter-rater agreement ($k = 0.32$) seen for this domain (Hartling *et al*., 2009).

Statistical significance testing between groups at baseline should not be performed in properly randomised trials, either by trialists or by systematic review authors. When there is uncertainty over the methods of randomisation, such testing may in theory have value in a systematic review context, but must be interpreted appropriately. Presence of statistically significant differences may be due to chance as well as to weaknesses in the methodology, and the absence of a statistically significant difference between groups by no means excludes the possibility of an important difference that may affect the trial's results. Instead, prognostic importance should be the main consideration. A large difference in an unimportant variable may be inconsequential, but a small, clinically-relevant difference in a key prognostic factor may be sufficient to affect inferences from the study. This is true regardless of the study sample size (Senn, 2012). Consequently, we suggest that both clinician advice and, when available, the results of studies that identify predictors of treatment response, or of studies of general prognosis, should form part of these considerations during systematic review protocol development. More generally, the implications of baseline imbalances in the trial outcomes being studied should always be considered, when this is possible. For example, if a treatment is evaluated on the basis of scores on a pain scale, then similarity of baseline pain scores is desirable.

Having performed assessments of baseline imbalances within individual trials, we hope that meta-analysts will also become aware of any important baseline differences across trials. This may enable them to make more informed judgements about when it is appropriate to combine studies in a meta-analysis, about the suitability of studies for subgroup or sensitivity analyses and about the generalisability (applicability) of meta-analytic results to other contexts.

Our suggestions for incorporating baseline information are not without challenges. There may be differences between treatment groups in unknown variables that affect prognosis that are not included in baseline characteristics tables. Judging a trial to be at low risk of selection bias on the basis of similarity in known variables would lead to unwarranted confidence in the findings of the trial. It may therefore be appropriate to draw a distinction between studies rated as at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies rated as at low risk of bias on the basis of baseline similarity alone. Another challenge is that adding an extra consideration would increase the amount of time taken to use the tool. Careful pre-specification both of the key prognostic variables and of the associated magnitude of an important difference also adds time to protocol development. Our proposed modifications are specific to trials reporting unadjusted analyses. When adjusted analyses are used, these may in theory overcome baseline imbalances due either to randomisation methods or to chance differences. Further consideration is needed of trials reporting adjusted analyses.

In offering advice to systematic reviewers that they incorporate assessment of baseline imbalance into risk of bias judgements, we have made suggestions to enhance future versions of the Cochrane risk of bias tool. Adoption of these suggestions has the potential for a reduction in uncertainty in systematic review conclusions,

and may reduce the risk that chance findings are interpreted as genuine treatment effects. They may also enable a more comprehensive use of available evidence, by allowing consideration of studies previously excluded from some reviews due to a lack of clarity about randomisation methods. Ideally, access to trial protocols and contact with trialists would resolve much of the (trial) methodological uncertainty encountered in systematic reviews. In reality, factors such as time and resource limitations, and obsolete investigator contact details, mean this is often not possible. The addition of trial protocol information to trial registration websites is an idea which should improve this situation. Until this happens, or until the reporting of randomised trial selection methods improves greatly, our suggestions offer a practical way of helping systematic reviewers perform selection bias assessments using all available information.

References

Adedoyin RA, Olaogun MOB, Fagbeja OO. 2002. Effect of interferential current stimulation in management of osteo-arthritic knee pain. *Physiotherapy* **88**: 493–99.

Austin PC, Manca A, Zwarenstein M, Juurlink DN, Stanbrook MB. 2010. A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals. *Journal of Clinical Epidemiology* **63**: 142–53.

Chapple CM. 2011. *Physiotherapy for Osteoarthritis of the Knee: Predictors of Outcome at One Year* [PhD]. University of Otago, Dunedin.

Clement ZV, Buckley N. 2011. Reporting of randomised controlled trials: before and after the advent of the CONSORT statement. *Journal of Clinical Medicine and Research* **3**: 28–34.

Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, *et al*. 2012, Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology* **79**: 785–92.

CONSORT. Transparent reporting of trials. [cited 16th November 2012]. Available from: http://www.consort-statement.org/.

Davey J, Turner RM, Clarke MJ, Higgins JP. 2011. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. *BMC Medical Research Methodology* **11**: 160.

Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Krebs Seida J, *et al*. 2009. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ* **339**: b4012.

Herbison P. 2012. Guest blog by Peter Herbison: what should be done with quasi-randomised trials? In: Cochrane Editorial Unit: The Cochrane Collaboration. Available from: http://www.editorial-unit.cochrane.org/blog/guest-blog-peter-herbison-what-should-be-done-quasi-randomised-trials.

Higgins JPT, Green S (eds). 2008. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley: England.

Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**: d5928.

Higgins JPT, Green S (eds). 2011. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from: www.cochrane-handbook.org.

Kuptniratsaikul V, Tosayanonda O, Nilganuwong S, Thamalikitkul V. 2002. The efficacy of a muscle exercise program to improve functional performance of the knee in patients with osteoarthritis. *Journal of the Medical Association of Thailand* **85**: 33–39.

Lund H, Weile U, Christensen R, Rostock B, Downey A, Bartels EM, *et al*. 2008. A randomized controlled trial of aquatic and land-based exercise in patients with knee osteoarthritis. *Journal of Rehabilitation Medicine* **40**: 137–44.

Mhaskar R, Djulbegovic B, Magazin A, Soares HP, Kumar A. 2012. Published methodological quality of randomized controlled trials does not reflect the actual quality assessed in protocols. *Journal of Clinical Epidemiology* **65**: 602–9.

National Collaborating Centre for Chronic Conditions. 2008. *Osteoarthritis: National Clinical Guideline for Care and Management in Adults*. Royal College of Physicians, London.

Senn S. 2012. Seven myths of randomisation in clinical trials. *Statistics in Medicine* **32**: 1439–50.

Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, *et al*. 2005. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Annals of the Rheumatic Diseases* **64**: 29–33.

Vale CL, Tierney JF, Burdett S. 2013. Can trial quality be reliably assessed from published reports of cancer trials: evaluation of risk of bias assessments in systematic reviews. *BMJ* **346**: f1798.

Method Note

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Quality assessment of comparative diagnostic accuracy studies: our experience using a modified version of the QUADAS-2 tool

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Assessing the quality of included studies is a vital step in undertaking a systematic review. The recently revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (QUADAS-2), which is the only validated quality assessment tool for diagnostic accuracy studies, does not include specific criteria for assessing comparative studies.

As part of an assessment that included comparative diagnostic accuracy studies, we used a modified version of QUADAS-2 to assess study quality. We modified QUADAS-2 by duplicating questions relating to the index test, to assess the relevant potential sources of bias for both the index test and comparator test. We also added review-specific questions.

We have presented our modified version of QUADAS-2 and outlined some key issues for consideration when assessing the quality of comparative diagnostic accuracy studies, to help guide other systematic reviewers conducting comparative diagnostic reviews.

Until QUADAS is updated to incorporate assessment of comparative studies, QUADAS-2 can be used, although modification and careful thought is required. It is important to reflect upon whether aspects of study design and methodology favour one of the tests over another.

Keywords: quality assessment; QUADAS; diagnostic accuracy; systematic review

Quality assessment of diagnostic accuracy studies

An important part of systematic review methodology is the assessment of the quality of the included studies, because it provides an indication of how reliable their results are likely to be. A number of different tools and checklists have been used in diagnostic systematic reviews (Whiting *et al*., 2005); however, the only validated quality assessment tool is the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool. The QUADAS tool was developed in 2003 (Whiting *et al*., 2003) and has recently been revised (QUADAS-2) (Whiting *et al*., 2011).

The QUADAS-2 tool was developed to improve the original QUADAS tool and to allow greater rating transparency. QUADAS-2 separates the evaluation of study quality into two main areas: risk of bias and concerns regarding applicability. The tool consists of four domains: patient selection, index test, reference standard, and flow and timing. For individual studies, each domain is assessed as being at a high, low or unclear risk of bias. The first three domains are also assessed in terms of applicability concerns using high, low or unclear ratings. The domains are supported by signalling questions, to help judge risk of bias and applicability concerns.

During development, one aim was to extend QUADAS-2 with a domain to assess studies comparing multiple index tests, and the tool was piloted on a review of such studies. However, the pilot revealed problems in applying this domain and also poor inter-rater reliability. Consequently, no criteria were included in QUADAS-2 to assess studies comparing multiple index tests (Whiting *et al*., 2011). Therefore, there is little published guidance available for researchers undertaking quality assessment of comparative diagnostic accuracy studies. The two main types of

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direct comparative diagnostic accuracy study are the crossover study, in which all patients undergo both tests and the reference standard, and the randomised controlled trial, in which patients are randomly allocated to receive the new test or the existing test as well as the reference standard. This article discusses quality items relating to these two study designs.

Although there is limited evidence on the specific sources of bias in comparative diagnostic accuracy studies, such studies still need to be quality-assessed. Therefore, the aim of this article is to highlight some of the issues to consider when assessing the quality of this type of study design when undertaking a systematic review. We also present more general thoughts on our experience of using QUADAS-2.

Systematic review of adjunctive colposcopy technologies

In 2011, the Centre for Reviews and Dissemination/Centre for Health Economics Technology Assessment Group was commissioned by the NHS National Institute for Health Research (NIHR) on behalf of the National Institute for Health and Clinical Excellence to undertake an assessment of adjunctive colposcopy technologies for examination of the uterine cervix. The assessment comprised of a systematic review and economic evaluation. To allow a comparison to be made between the new technologies and the current practice, only comparative studies were eligible for inclusion in the systematic review (studies comparing an adjunctive colposcopy technology with standard colposcopy, using histopathology of biopsy samples as the reference standard). We used a modified version of the QUADAS-2 tool to assess the quality of the included studies. Because the QUADAS-2 tool does not include specific guidance for the assessment of comparative diagnostic accuracy studies, we modified the tool to accommodate this research design. A full description of the systematic review methods is published in a Health Technology Assessment (HTA) report (Wade *et al*., 2013).

Modifications made to QUADAS-2

The developers of QUADAS-2 recommend that the tool is tailored for each specific review by adding or omitting signalling questions (used to assist judgements); we added review-specific questions to the domains relating to the index test and the reference standard. We also duplicated signalling questions relating to the index test domain, to assess the relevant potential sources of bias for both the index test and the comparator test. An overall risk of bias assessment and an applicability assessment were also determined for the index test domain for both the index test and comparator test. Our modified version of the QUADAS-2 tool is shown in Figure 1.

One question in the original QUADAS tool, which was removed during the development of QUADAS-2, asked whether the same clinical data were available when the test results were interpreted as would be available when the test is used in practice; this question was particularly relevant for our assessment, because the evaluation of colposcopy results is almost always influenced by knowledge of previous clinical data (e.g. cytology/human papillomavirus test results), so we reinstated this question. Across studies, it is possible that variation or bias in results may arise because of some studies using such clinical information and others not. Patients acted as their own controls in the studies in our review, so knowledge of this information would be very unlikely to bias results comparing tests within a study. However, studies that did use prior clinical data would benefit from having low applicability concerns, whereas for those which did not, the applicability concerns would be high.

We also asked whether the execution of the index test, comparator test and reference standard was as it would be in practice, and whether the colposcopists undertaking the tests were experienced in colposcopy and had been given training/experience in using the new technology. Three further questions were assessed: (i) whether a sample size calculation was used (which relates more to precision, than to bias or applicability); (ii) whether the data were analysed by lesion, patient or both; and (iii) whether results for all prespecified outcomes were reported. We also allowed 'any other comments' relating to other quality concerns to be recorded.

The modified QUADAS-2 tool was piloted prior to use. The assessment was performed by one reviewer, and independently checked by a second; disagreements were resolved through consensus. Where data were missing from publications or other study reports, the authors were contacted.

Our experience of using QUADAS-2

Six comparative diagnostic accuracy studies met the inclusion criteria for the review. Poor reporting and limited feedback from authors limited the quality assessment of some of the included studies, resulting in many aspects of study quality being assessed as 'unclear'. Full results of the quality assessment are reported in an appendix of the HTA report (Wade *et al*., 2013).

The QUADAS-2 tool was considered to be more time consuming to complete than the original QUADAS tool, as more 'free text' is recorded to justify risk of bias/applicability assessments. However, this additional detail was useful when reflecting on the overall quality of the study.

STUDY ID:

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection:

Was a consecutive or random sample of patients enrolled?
Yes/No/Unclear

Was a case-control design avoided?
Yes/No/Unclear

Did the study avoid inappropriate exclusions?
Yes/No/Unclear

Could the selection of patients have introduced bias?
RISK OF BIAS: LOW/HIGH/UNCLEAR

Are there concerns that the included patients and setting do not match the review question?
APPLICABILITY CONCERS: LOW/HIGH/UNCLEAR

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted:

Were the index test results interpreted without knowledge of the results of the reference standard?
Yes/No/Unclear

If a threshold was used, was it pre-specified?
Yes/No/Unclear

*†Was the execution of the intervention technology as it would be in practice?
Yes/No/Unclear

*†Was the execution of the comparator technology as it would be in practice?
Yes/No/Unclear

*†Were the colposcopists undertaking the tests experienced in colposcopy
(i.e. accredited and with at least one year's experience)?
Yes/No/Unclear

*†Were the colposcopists undertaking the new technologies given training/experience in the new technology?
Yes/No/Unclear

‡Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?
Yes/No/Unclear

Could methods used to conduct or interpret the index test have introduced bias?
†INDEX TEST RISK OF BIAS: LOW/HIGH/UNCLEAR

†COMPARATOR TEST RISK OF BIAS: LOW/HIGH/UNCLEAR

Are there concerns that the index test, its conduct, or interpretation differ from the review question?
†INDEX TEST APPLICABILITY CONCERNS: LOW/HIGH/UNCLEAR

†COMPARATOR TEST APPLICABILITY CONCERNS: LOW/HIGH/UNCLEAR

Figure 1. Modified QUADAS-2 tool

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted:

Is the reference standard likely to correctly classify the target condition?
Yes/No/Unclear

Were the reference standard results interpreted without knowledge of the results of the index test?
Yes/No/Unclear

*Was the execution of the reference standard as it would be in practice?
Yes/No/Unclear

Could methods used to conduct or interpret the reference standard have introduced bias?
RISK OF BIAS: LOW/HIGH/UNCLEAR

Are there concerns the target condition as defined by the reference standard does not match the question?
APPLICABILITY CONCERNS: LOW/HIGH/UNCLEAR

DOMAIN 4: FLOW AND TIMING

Draw a flow-chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2x2 table:

Describe the time interval between index test and reference standard and any actions taken:

Was there an appropriate interval between index test and reference standard?
Yes/No/Unclear

Did all patients receive the same reference standard?
Yes/No/Unclear

Were all patients included in the analysis?
Yes/No/Unclear

Bias: Could the patient flow have introduced bias?
RISK OF BIAS: LOW/HIGH/UNCLEAR

***ADDITIONAL QUALITY ASSESSMENT QUESTIONS:**

1) Was a sample size calculation used?
Yes/No/Unclear

2) Were the data analysed by lesion, patient or both?
Lesion/Patient/Both/Unclear

3) Were results for all pre-specified outcomes reported?
Yes/No/Unclear

4) Any other comments?

* Questions added

† Question repeated to reflect comparative study design

‡ Question reinstated from original QUADAS tool

Figure 1. Continued

The signalling questions were also helpful in drawing conclusions about the overall risk of bias and applicability concerns. We considered whether the responses to the signalling questions resulted in potential bias favouring one technology over the other, when making overall judgements on domains. However, there is inevitably a degree of subjectivity when deciding appropriate levels of risk of bias and applicability concerns. When making assessments, we were aware that it is unlikely that a study can be interpreted as having no risk of bias, and that judging a study as being at 'high risk' because of a minor risk to bias is not very informative and, worse still, may be an unfair representation of the test in question.

We could not assess the inter-rater reliability of the tool because one reviewer performed the assessment and another checked it (as specified in our systematic review protocol). However, the developers of QUADAS-2 reported considerable variation in the levels of inter-rater agreement on bias and applicability between the reviewers who piloted it (Whiting *et al*., 2011), particularly for risk of bias, where the percentage of agreement across individual domains ranged from 25% to 100%. Perhaps an intermediate option between 'low risk' and 'high risk', or more specific guidance on what might constitute a high or low risk grading, might promote consistency in future versions of QUADAS.

The summary table suggested by the developers of QUADAS-2 enabled a clear and concise presentation of the results of the quality assessment (Wade *et al*., 2013). We found that the advice of our clinical advisor was essential in answering topic-specific questions relating to applicability and would advise against using the tool without clinical input.

Issues relating specifically to comparative studies

In Table 1 we have outlined some key questions that reviewers might consider incorporating into a modified version of QUADAS-2, some of which warrant discussion in more detail. Our systematic review did not include any diagnostic randomised controlled trials. However, for reviews that include this study design, additional issues need to be considered, such as whether the methods used to generate the allocation sequence and conceal the allocation of tests were likely to have caused biased patient selection (Question 1).

If interpretation of test results involves subjective assessment, it may be important to consider whether the order in which the tests are undertaken could introduce bias (Question 2). Is there a need for randomisation of test order, or for blinding of assessors to the results of the other index test (i.e. separate assessors for each index test)? For example, in our review, the results of one test (DySIS) were objective (recorded by software, according to predetermined cut-offs), and those of standard colposcopy were subjective, meaning there was only one viable option for determining test order (obviating the need for either randomisation or blinding).

Another aspect to consider is whether the results of both index tests were verified using the same reference standard (Question 7). In one of the studies in our review, patients who had an abnormal comparator test result underwent biopsy as the reference standard. For all other assessment results, endocervical curettage (or, occasionally, diagnostic excision biopsy) was performed as the reference standard. This was the case irrespective of the result of the index test. Furthermore, although assessment was also made at the 2-year follow-up point, this may not have captured some of the initial assessment false-negative results, because diseased areas can recover over time.

Consideration of uninterpretable results (Question 10) can be challenging for systematic reviewers, and raises issues that are related to both the unmodified QUADAS-2 (signalling Question 3 of Domain 4:'*Were all patients included in the analysis?*') and to the assessment of randomised trial attrition bias using the Cochrane risk of bias tool (Higgins *et al*., 2011). A study evaluating the Cochrane risk of bias tool found only 'fair' inter-rater agreement ($k = 0.32$) for attrition bias, highlighting the difficulties involved (Hartling *et al*., 2009). Similar to randomised trial evaluations, for diagnostic studies, the focus should be on the reasons for the results and the extent to which the reasons differed between tests. Reviewers should also check that data are reported as absolute and not just relative differences.

It is difficult to record these issues, even in a modified version of QUADAS-2; we tacitly recorded many of them (via the free text area available for each domain) and were aware of them in the context of the overall reliability of a study, although (for most issues) we did not attempt to formally assess them using signalling questions. If three or more tests are being compared, it may be even more difficult to attempt to incorporate these comparative issues into the current QUADAS format.

Conclusions

Until QUADAS is updated to incorporate assessment of comparative studies, QUADAS-2 can be used, although modification and careful thought is required. It is important to reflect upon whether aspects of study design and methodology favour one of the tests over another. In this article, we have documented these aspects on the basis of both our own recent review experience and on further consideration of the relevant issues. We hope that the suggested areas for assessment we have outlined will inform both other systematic reviewers conducting comparative diagnostic reviews and the development of future versions of QUADAS.

Table 1. Study quality aspects to consider when conducting a systematic review of comparative diagnostic accuracy studies

Question	Domain*	Issues to consider
1. If diagnostic randomised controlled trials are included in the review, were appropriate methods used to generate the allocation sequence and conceal the allocation of tests?	1	Consider whether the methods used may have resulted in biased patient selection. Both randomisation method details and result details can be used to assess risk of bias. If, at baseline, important prognostic factors are balanced across groups, patient selection can be judged as being at low risk of bias (even if the method of reporting is unclear).
2. Were the index test results interpreted without knowledge of the results of the comparator test (and vice versa)?	2	Were blinding or randomisation methods used? If not, were they needed? Did the individual tests require objective or subjective interpretation?
3. Were investigators appropriately experienced (established tests) and trained (new tests) to adequately perform both tests?	2	Accreditation, number of years of experience and number of procedures/tests performed. Time spent on training. Manufacturer guidance on training.
4. Was the execution of both tests as they should be performed in clinical practice?	2	Manufacturer guidance on appropriate test use. Atypical methods/procedures used? Current good practice guidance used?
5. Were the index and the comparator tests independent?	2	Did one test form part of another?
6. Were the reference standard and the index/comparator tests independent of each other?	3	Did the index or comparator test form part of the reference standard?
7. Were the results of both tests verified using the same reference standard?	4	The reference standard used may vary depending on individual patient test results. For example, some may have biopsy or further tests, whereas others may just have a follow-up visit at a much later date.
8. Was there an appropriate interval between the index and the comparator tests?	4	Rate of disease development. Possibility of disease status change (improvement or deterioration).
9. Did the whole sample undergo both tests (or one test, if study was randomised)?	4	Consider whether differences in test characteristics might result in differences in drop-out rates.
10. Was there a difference in the number of uninterpretable or indeterminate results between tests, which is likely to have biased the study results?	4	Reasons for such results could be related to test or patient characteristics (possible bias issue) or could be due to chance, for example, equipment failure, which may be common when using developing technology (although this will reduce study power, it is unlikely to be an important bias issue).

*1, Patient selection; 2, Index test; 3, Reference standard; 4, Flow and timing. All questions relate to bias; Questions 3 and 4 also relate to applicability.

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References

Whiting P, Rutjes AW, Dinnes J, Reitsma JB, Bossuyt PM, Kleijnen J. 2005. A systematic review finds that diagnostic reviews fail to incorporate quality despite available tools. *Journal of Clinical Epidemiology* **58**: 1–12.

Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. 2003. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* **3**: 25.

Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al*. 2011. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* **155**: 529–36.

Wade R, Spackman E, Corbett M, Walker S, Light K, Naik R, *et al*. 2013. Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS, LuViva Advanced Cervical Scan and Niris Imaging System: a systematic review and economic evaluation. *Health Technology Assessment* **17**(8): 1–240.

Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**: d5928.

Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Seida JK, *et al*. 2009. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ* **339**: b4012.

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Randomization methods in emergency setting trials: a descriptive review

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Background: **Quasi-randomization might expedite recruitment into trials in emergency care settings but may also introduce selection bias.**

Methods: **We searched the Cochrane Library and other databases for systematic reviews of interventions in emergency medicine or urgent care settings. We assessed selection bias (baseline imbalances) in prognostic indicators between treatment groups in trials using true randomization versus trials using quasi-randomization.**

Results: **Seven reviews contained 16 trials that used true randomization and 11 that used quasi-randomization. Baseline group imbalance was identified in four trials using true randomization (25%) and in two quasi-randomized trials (18%). Of the four truly randomized trials with imbalance, three concealed treatment allocation adequately. Clinical heterogeneity and poor reporting limited the assessment of trial recruitment outcomes.**

Conclusions: **We did not find strong or consistent evidence that quasi-randomization is associated with selection bias more often than true randomization. High risk of bias judgements for quasi-randomized emergency studies should therefore not be assumed in systematic reviews. Clinical heterogeneity across trials within reviews, coupled with limited availability of relevant trial accrual data, meant it was not possible to adequately explore the possibility that true randomization might result in slower trial recruitment rates, or the recruitment of less representative populations.** © 2015 The Authors. ***Research Synthesis Methods*** **published by John Wiley & Sons, Ltd.**

Keywords: baseline imbalance; emergency setting; quasi-randomization; randomization; selection bias

1. Background

Recruitment to emergency medicine clinical trials may be complicated by the short time frames available for obtaining consent and for identifying, enrolling, randomizing and treating eligible participants (Cofield *et al*., 2010). Possible drawbacks of using methodologically sound randomization processes in emergency settings (such as telephone or web-based systems, or systems using sequentially numbered sealed, opaque envelopes) might be a delay in treatment, and complexity of trial administration (Zhao *et al*., 2010). Recruitment difficulties can arise where treatment delays are clinically unacceptable. Trial investigators may therefore sometimes need to consider adopting more pragmatic approaches to recruitment that involve balancing methodological rigour with expediency in enrolment and randomization.

One approach that has been used with the aim of reducing delay in enrolment is a 'quasi-random' allocation of treatment. This involves the use of a pre-defined participant or setting characteristic, such as date of birth, to determine which treatment a participant receives. The major concern when using quasi-randomization is that trial investigators have prior knowledge of the treatment that an individual is due to receive. This lack of allocation

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concealment increases the risk of selection bias during the trial recruitment phase. Selection bias would be expected to adversely impact trial validity if it introduced an imbalance between trial treatment groups in an important prognostic indicator. Important baseline imbalances can also arise by chance, especially when sample sizes are small. Regardless of cause, such imbalances can make it difficult to ascribe any outcome effects to trial interventions alone.

Systematic reviews that appraise and synthesize evidence from clinical trials deal with quasi-randomization in different ways. Review authors may decide *a priori* to exclude quasi-randomized trials, or they may opt to include them with pre-specified plans for subgroup analyses, usually based on adequacy of allocation concealment. When quasi-randomized trials are included in systematic reviews, their findings may be undervalued, because they are almost always automatically judged to be at high risk of selection bias, even though evidence of actual selection bias is either not sought or may not be apparent (Corbett *et al*., 2014).

This study had two main objectives, both relating to clinical trials performed in an emergency or urgent care setting. Firstly, we aimed to obtain an estimate of the prevalence of important baseline imbalances that may have been a consequence of selection bias, in trials that used quasi-randomization versus those that used true randomization. Secondly, we wished to examine whether there is any evidence to suggest that any possible benefits of using true randomization might be offset in other areas of trial recruitment, such as slower recruitment rates, or the recruitment of less representative populations.

2. Methods

In December 2013, we used two approaches to identify relevant systematic reviews. First, we searched the reviews included in an overview of reviews project (ongoing at the Centre for Reviews and Dissemination (CRD)), which is evaluating reviews of delivery room interventions. Second, we identified systematic reviews classified as 'emergency medicine' in the Cochrane Library. Eligible reviews had to include at least one clinical trial that clearly reported using true randomization and at least one quasi-randomized trial that clearly reported how interventions were allocated to patients. We defined quasi-randomization as allocation methods that use easily accessible information such as patient hospital number, date of birth and date of admission, or by using alternate allocation. For the purposes of this study, we defined true randomization as sequence generation using a method that has a random component, regardless of the level of allocation concealment; we did this because in systematic reviews, eligibility of trial design is often based on whether random sequence generation methods were used. We then distinguished between the true randomized trials that used adequate allocation concealment methods, from those using inadequate allocation concealment methods. Where closely related reviews were identified, across which there was overlap of trials, we selected the review with the largest number of quasi-randomized trials.

Eligible trials had to include participants with acute injury or illness, requiring immediate intervention as quickly as was clinically practicable. In the event of any uncertainty regarding how quickly the intervention was given, a decision on eligibility for our study was made based on the type of consent obtained; studies using time-saving strategies such as waived, deferred or implied consent were included, and studies requiring (pre-randomization) patient consent were excluded. Trials of prophylactic interventions or surgery/post-surgery interventions were excluded. Cross-over trials, cluster-randomized trials and trials that were reported only as conference abstracts were also excluded. One particular investigator has performed many trials in emergency settings, most of which have since been retracted; all studies by this author were deemed ineligible for this study (Oransky, 2013).

We included all the quasi-randomized trials in eligible systematic reviews. In reviews where the total number of studies was $\leq$10, we included all eligible trials providing the ratio of randomized to quasi-randomized studies was not greater than 2:1. Where higher than a 2:1 ratio existed and the total number of studies in the review was $\leq$10, we achieved a 2:1 ratio by selecting the most recently published truly randomized trials.

For reviews with more than 10 studies in total, we selected an equal number of true and quasi-randomized trials, again by prioritizing those published most recently. For example, for a review with five quasi-randomized controlled trials (RCTs) and 25 trials with true randomization, we would select all five quasi-RCTs. We would then select the five most recently published eligible trials that used true randomization.

Evidence of possible selection bias was sought by assessing baseline imbalances in important prognostic indicators across treatment groups within individual trials (Corbett *et al*., 2014). Two authors (W. M. and S. O.) provided advice on the important prognostic indicators for neonatal trials (including references for relevant studies); for the remaining trials, information from published studies was identified. These approaches were also used to define what constituted an important baseline difference between trial treatment groups. When necessary, we made arbitrary but conservative judgements on cut-offs.

For each trial, we extracted the following data: methods of sequence generation and allocation concealment (including any reasons given for using quasi-random methods), trial eligibility criteria and corresponding details of the populations enrolled, the target number of patients to recruit and the number actually recruited, the number of eligible patients who were not enrolled (with reasons), the number of ineligible patients enrolled, data to calculate an estimate of the rate of recruitment (per centre), type of consent obtained and the country/countries where the trials were performed. We made risk of bias judgements on methods of allocation

concealment using information from both the published trial reports and the systematic reviews. One author extracted data that were independently checked by a second author.

3. Results

We identified seven eligible systematic reviews, including 27 eligible clinical trials: 11 used quasi-random methods, and 16 used true randomization. Of the seven included reviews, three were of fluid resuscitation for critically ill patients (Kwan *et al*., 2003, Bunn *et al*., 2004, Perel and Roberts, 2011), two were of neonatal interventions (one investigating respiratory oxygen levels (Saugstad *et al*., 2008) and one the effect of intubation (Halliday and Sweet, 2001)), one was of intubation for adults or children (Lecky *et al*., 2008) and one was of hypothermia following cardiopulmonary resuscitation (Arrich *et al*., 2009). Six of the 11 quasi-randomized trials did not report a rationale for using quasi-randomization (Caldwell and Bowser, 1979, Linder *et al*., 1988, Ramji *et al*., 1993, Evans *et al*., 1996, Gausche *et al*., 2000, Rabitsch *et al*., 2003). Three trials stated that quasi-randomization was used to avoid detrimental delay in care (Bickell *et al*., 1994, Ramji *et al*., 2003, Bajaj *et al*., 2005); a fourth trial also stated this reason adding a desire to avoid a reduction in the recruitment of the most depressed infants (possibly leading to a non-representative sample; Saugstad *et al*., 1998). One trial viewed quasi-randomization as being the only feasible method for immediate use by large numbers of ambulance officers and emergency department physicians (Bernard *et al*., 2002).

Details of individual trials (with a full trial reference list) are reported in Supporting information S1. The important prognostic indicators identified for each systematic review are listed in Supporting information S2, which also details the associated magnitudes of group difference used to decide whether a trial had an important baseline imbalance.

The methods and results of randomization in the included clinical trials are listed in Table 1; details on the methods used for sequence generation and allocation concealment in each trial are available in Supporting information S1. Important imbalance between groups within a trial was identified in two of the 11 quasi-randomized trials (18%) and four of the 16 trials using true randomization (25%); these trials are presented in bold in Table 1. In the four trials that used true randomization that had imbalance, three described appropriate methods to conceal treatment allocation, and one used an inappropriate method.

An assessment of how representative the trial populations were could only be made for the review of resuscitation approaches in newborns (Saugstad *et al*., 2008). Eligibility criteria with respect to weight and age varied between trials: all the quasi-randomized studies had no age criteria and very broad weight criteria (all using $\geq$1000 g); all the truly randomized trials recruited only term infants (except for one trial that recruited infants $>$34 weeks), with no specific weight criteria.

Table 2 summarizes the trial accrual and recruitment data. In two reviews, quasi-randomization was associated with faster accrual, with recruitment rates being double (Lecky *et al*., 2008) and triple (Halliday and Sweet, 2001) those achieved in equivalent trials using true randomization. In two reviews, there was little or no indication of differences in accrual rates (Saugstad *et al*., 2008, Arrich *et al*., 2009) although for one of these reviews it was not possible to estimate monthly accrual rates in half the trials (Saugstad *et al*., 2008). Clinical and methodological heterogeneity across trials precluded any meaningful comparisons in the remaining reviews (Kwan *et al*., 2003, Bunn *et al*., 2004, Perel and Roberts, 2011). Data on how many eligible patients were not recruited and on how many ineligible patients were recruited were often not reported.

4. Discussion

This descriptive review of emergency care setting clinical trials did not find any evidence that quasi-randomization results in selection bias more often than true randomization; these results suggest that high risk of bias judgements for quasi-randomized studies should therefore not be assumed in systematic reviews of interventions delivered in emergency or urgent care settings.

Important imbalance between groups within a trial was identified in two of the 11 quasi-randomized trials (18%) and four of the 16 trials using true randomization (25%). These results suggest that when baseline imbalance does occur, it may be a consequence of chance effects, which become evident (and problematic) because of the small trial populations. Three trials had important baseline imbalances despite using both true randomization and adequate allocation concealment methods. All three had small group sizes – having 50 or fewer participants per arm. Chance imbalances may be more prevalent in small emergency setting trials because of difficulties in implementing methods to reduce the possibility of imbalances. The use of stratified or minimization randomization methods is likely to be impractical in most emergency settings, although feasible in some (Zhao *et al*., 2010).

Possible reasons for the low incidence of selection bias in emergency setting trials might include the following: lack of (pre-intervention) time for trial investigators/staff to judge prognosis; investigators being less inclined to allow their biases to influence the care of such acutely ill patients; the possibility of regulatory authority audit (and having to justify inappropriate exclusions); the team nature of intervention delivery, precluding opportunities

Table 1. Trial randomization methods and baseline similarity of groups.

Trial	Sequence generation method[a]	Risk of bias from allocation concealment methods[a]	Important imbalance identified?[b]	Number randomized (number of groups)
Review: Resuscitation of newborns with room air or pure oxygen (Saugstad et al., 2008)				
Bajaj *et al.*, 2005	Quasi-random	High	No	204 (2)
Ramji *et al.*, 1993	Quasi-random	High	No	84 (2)
Ramji *et al.*, 2003	Quasi-random	High	No	433 (2)
Saugstad *et al.*, 1998	Quasi-random	High	No	703 (2)
Toma, 2006a	Truly random	Unclear	No	54 (2)
Toma, 2006b	Truly random	Unclear	No	44 (2)
Toma, 2007	Truly random	Unclear	No	56 (2)
Vento, 2001	Truly random	Unclear	No	527 (2)
Vento, 2003	Truly random	Unclear	No	151 (2)
Vento, 2005	Truly random	Unclear	No	53 (2)
Review: Endotracheal intubation in meconium-stained newborns (Halliday and Sweet, 2001)				
Linder *et al.*, 1988	Quasi-random	High	No	572 (2)
Wiswell *et al.*, 2000	Truly random	High	Unclear	2094 (2)
Review: Colloids versus crystalloids for fluid resuscitation in critically ill patients (Perel and Roberts, 2011)				
Evans *et al.*, 1996	Quasi-random	High	No	25 (2)
Bulger *et al.*, 2011	Truly random	Low	No	895 (3)
James *et al.*, 2011	**Truly random**	**Low**	**Yes**	**115 (4)**
Review: Timing and volume of fluid administration for patients with bleeding (Kwan et al., 2003)				
Bickell *et al.*, 1994	Quasi-random	High	No	598 (2)
Dutton, 2002	Truly random	Low	No	110 (2)
Turner *et al.*, 2000	Truly random	High	No	1309[c] (2)
Review: Hypertonic versus near isotonic crystalloids for fluid resuscitation in critically ill patients (Bunn et al., 2004)				
Caldwell and Bowser, 1979	Quasi-random	High	Unclear	37 (2)
Cooper *et al.*, 2004	Truly random	Low	No	229 (2)
Vassar *et al.*, 1993	**Truly random**	**Low**	**Yes**	**233 (4)[d]**
Review: Hypothermia for neuroprotection after cardiopulmonary resuscitation (Arrich et al., 2009)				
Bernard *et al.*, 2002	**Quasi-random**	**High**	**Yes**	**84 (2)**
HACA, 2002	Truly random	Low	No	275 (2)
Laurent, 2005	**Truly random**	**Low**	**Yes**	**61 (3)**
Review: Intubation for acutely ill and injured patients (Lecky et al., 2008)				
Gausche *et al.*, 2000	Quasi-random	High	No	830 (2)
Rabitsch *et al.*, 2003	**Quasi-random**	**High**	**Yes**	**172 (2)**
Goldenberg, 1986	**Truly random**	**High**	**Yes**	**175 (2)**

[a]See Supporting information S1 for details.
[b]See Supporting information S1 and S2 for details.
[c]Paramedics were randomized, with 1309 patients subsequently recruited.
[d]Baseline data only presented for 194 patients (as 39 were ineligible).

for bias; and the fact that interventions may be administered by staff with limited involvement in trial design (e.g. paramedics) who might be less likely to have strong enough opinions to result in biased selection. Emergency setting trials are also quite likely to assess mortality or other objectively assessed outcomes; trials with inadequate or unclear allocation concealment show no evidence of bias for all-cause mortality, and little evidence of bias for objective outcomes (Wood *et al.*, 2008).

Clinical heterogeneity across trials within reviews, coupled with a shortage of quasi-randomized trials, meant it was only possible to examine one review to evaluate whether population variability differed between the different randomization approaches. Furthermore, accrual and recruitment data were often unavailable. The degree of recruitment of ineligible patients was not well documented in several trials, although in those not reporting any actual data it was nevertheless evident from the methods used that some trials must have randomized many ineligible patients. Practices such as sealed envelopes being assigned to the records of expectant mothers on admission (before eligibility can be known), and the discarding of randomization assignments when infants were not eligible, were evident in neonatal trials (Wiswell *et al.*, 2000, Vento *et al.*, 2003).

Our study has some limitations, the main one being that it was quite small and was exploratory in nature. In terms of assessing biases within trials, we investigated only the impact of randomization methods on selection bias and did not attempt to evaluate other biases that might result from the randomization methods. It was our intention, when planning the study, that we would also try to compare outcome results data across the

Table 2. Trial accrual and recruitment data.

Trial	Sequence generation method	Target sample size	Patients randomized	RA rate[a]	No. of eligible patients not randomized	No. of ineligible patients randomized
Review: Resuscitation of newborns with room air or pure oxygen (Saugstad et al., 2008)						
Bajaj *et al.*, 2005	Quasi-random	146	204	14	0	0
Ramji *et al.*, 1993	Quasi-random	72	84	–[c]	0	0
Ramji *et al.*, 2003	Quasi-random	300	433	4	0	2
Saugstad *et al.*, 1998	Quasi-random	648	703	3	107	90
Toma, 2006a	Truly random	NR	54	–[c]	NR	NR
Toma, 2006b	Truly random	NR	44	15	NR	NR
Toma, 2007	Truly random	NR	56	–[c]	NR	NR
Vento, 2001	Truly random	NR	527	–[c]	NR	NR
Vento, 2003	Truly random	NR	151	–[c]	NR	24
Vento, 2005	Truly random	NR	53	1	Unclear, although 3 'improperly randomized'	0
Review: Endotracheal intubation in meconium-stained newborns (Halliday and Sweet, 2001)						
Linder *et al.*, 1988	Quasi-random	NR	572	18	0	0
Wiswell *et al.*, 2000	Truly random	2058	2094	6	NR	Unclear
Review: Colloids versus crystalloids for fluid resuscitation in critically ill patients (Perel and Roberts, 2011)						
Evans *et al.*, 1996	Quasi-random	NR	25	25	NR	0
Bulger *et al.*, 2011	Truly random	3726	895	0.3	NR	23
James *et al.*, 2011	Truly random	140	115	3	0	5
Review: Timing and volume of fluid administration for patients with bleeding (Kwan et al., 2003)						
Bickell *et al.*, 1994	Quasi-random	~600	598	16	0	471
Dutton, 2002	Truly random	NR	110	6	NR	NR
Turner *et al.*, 2000	Truly random	NR[b]	1309	5	0	0
Review: Hypertonic versus near isotonic crystalloids for fluid resuscitation in critically ill patients (Bunn et al., 2004)						
Caldwell and Bowser, 1979	Quasi-random	NR	37	1	NR	NR
Cooper *et al.*, 2004	Truly random	220	229	0.5	0	0
Vassar *et al.*, 1993	Truly random	600	233	2	0	39
Review: Hypothermia for neuroprotection after cardiopulmonary resuscitation (Arrich et al., 2009)						
Bernard *et al.*, 2002	Quasi-random	62	84	0.6	0	0
HACA, 2002	Truly random	NR	275	0.6	30	0
Laurent, 2005	Truly random	90	61	1	0	0
Review: Intubation for acutely ill and injured patients (Lecky et al., 2008)						
Gausche *et al.*, 2000	Quasi-random	800	830	–[c]	1	None
Rabitsch *et al.*, 2003	Quasi-random	NR	172	14	NR	NR
Goldenberg, 1986	Truly random	NR	175	7	0	~10

RA, randomization; NR, not reported.
[a]Estimated monthly rate, per centre.
[b]Not reported for patients but 420 for paramedics.
[c]Unable to calculate an estimate.

different methods of randomization. However, it became apparent during piloting that there was too much variation in the outcomes reported to make this a worthwhile exercise. Furthermore, we were aware that other possible biases (e.g. lack of blinding of the treating clinician) will have sometimes differed between the types of randomization method, which may also have had an impact on effect estimates. Our focus was therefore on selection bias and on how this may be assessed in systematic reviews. Although our lists of prognostic indicators and cut-offs were thorough and quite conservative (i.e. small differences were flagged as being potentially important), they were nevertheless devised pragmatically, with the main aim being to compare the two methods of randomization. Our study relates only to imbalances in known prognostic indicators; the possibility of selection bias resulting in imbalances in unknown prognostic factors remains for quasi-randomized trials, but not for truly randomized trials (Urbach, 1993, Worrall, 2002).

Our results provide supportive evidence for the idea of systematic reviewers utilizing data on important baseline covariates when judging risk of selection bias in clinical trials, rather than using randomization method details alone; the results also highlight the value of assessing for chance imbalances (Corbett *et al*., 2014). Selection bias was not evident in eight of the 11 quasi-randomized trials included in our study; all eight would normally have been judged as being at high risk of bias. The results from our study also help to inform consideration and discussion about why quasi-randomized trials are excluded from systematic reviews (Herbison, 2012). It is unclear why trials that use true randomization, but inadequate allocation concealment, are frequently deemed to be more suitable for inclusion than quasi-randomized trials. One further issue arose to help inform future systematic reviews of emergency setting interventions: considering the difficulties that may be encountered when recruiting participants into emergency setting trials, we suggest that an assessment of the external validity and applicability of trial results is essential. Such assessments may be complex, which may partly explain why they are often neglected in systematic reviews (Dekkers *et al*., 2010, Burchett *et al*., 2011).

In one of the truly randomized trials in our study, a delay in administering treatment was avoided by opening envelopes before eligibility could be confirmed (Wiswell *et al*., 2000); another trial saved time by randomizing paramedics, rather than patients (Turner *et al*., 2000). However, the use of these methods meant that allocation was not properly concealed and eligible patients could potentially have then been wrongly excluded (because eligibility assessments would have been performed with foreknowledge of the allocated treatment). Nevertheless, in some trials, methodologically sound randomization was used without causing delays in treatment. This was evident in the fluid resuscitation reviews; in many of the trials, the randomization sequence was applied (in code) physically to the interventions (the bags of fluid; Mattox *et al*., 1991, Bulger *et al*., 2011, James *et al*., 2011, Cooper *et al*., 2004, Vassar *et al*., 1993). This appears to be a time-saving and resource-efficient method that would obviate the need for quasi-random methods (assuming good trial administration, with the supply of code-labelled bags not running out at any point). However, of the trials in the remaining reviews in our study, such methods were not an option, because the interventions could not be delivered in discrete packs.

Considering the reporting limitations seen in many of the trials in our study, further methodological research might best be focussed only on evaluating baseline imbalance outcomes in populations that are relatively simple to define prognostically, such as preterm neonates or trauma patients. Future studies might also identify how frequently chance imbalances arise in neonatal or trauma trials using methodologically sound randomization methods, regardless of level of emergency status. Assessment of whether minimization or stratified randomization techniques have been used or whether statistically adjusted results (to allow for the effect of confounders) have been calculated would also be informative. In terms of clinical research, an example area where quasi-randomization might be considered to help simplify and facilitate trial recruitment is the effect of timing on umbilical cord clamping in preterm infants; a Cochrane review has concluded that there were insufficient data for all the review's primary outcomes, despite an evidence base of 15 randomized trials, which were mostly small studies (Rabe *et al*., 2012). Although our results relate to emergency setting clinical trials, the use of randomized trials has expanded to areas of study beyond clinical medicine; our results may be of interest to any investigators who are studying interventions that are given in time-limited settings.

5. Conclusion

This descriptive review of emergency care setting clinical trials did not find any evidence that quasi-randomization results in selection bias more often than true randomization; these results suggest that high risk of bias judgements for quasi-randomized studies should therefore not be assumed in systematic reviews of interventions delivered in emergency or urgent care settings.

Our results also suggest that the likelihood of chance imbalances affecting trial results may also be an important issue to consider, for both trial investigators and systematic reviewers. Clinical heterogeneity across trials within reviews, coupled with limited availability of relevant trial accrual data, meant it was not possible to adequately explore the possibility that true randomization might result in slower trial recruitment rates, or the recruitment of less representative populations.

Ethical approval

None required.

Conflict of interests

The authors declare that they have no competing interests.

Authors' contributions

M. C. conceived of the study, developed its design and coordination, identified studies, extracted and analysed the data, drafted the manuscript and coordinated the authors' comments. T. M. B. helped to identify relevant studies, extracted data and helped to revise the manuscript. W. M. participated in the design of the study, provided clinical advice, contributed to the interpretation of data and helped to revise the manuscript. S. O. provided clinical advice, contributed to the interpretation of data and helped to revise the manuscript.

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References

Arrich J, Holzer M, Herkner H, Mullner M. 2009. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database of Systematic Reviews* **9**: CD004128.

Bajaj N, Udani RH, Nanavati RN. 2005. Room air vs. 100 per cent oxygen for neonatal resuscitation: a controlled clinical trial. *Journal of Tropical Pediatrics* **51**: 206–211.

Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. 2002. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *The New England Journal of Medicine* **346**: 557–563.

Bickell WH, Wall MJ Jr, Pepe PE Jr, Martin RR, Ginger VF, Allen MK, Mattox KL. 1994. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *The New England Journal of Medicine* **331**: 1105–1109.

Bulger EM, May S, Kerby JD, Emerson S, Stiell IG, Schreiber MA, Brasel KJ, Tisherman SA, Coimbra R, Rizoli S, Minei JP, Hata JS, Sopko G, Evans DC, Hoyt DB, Investigators ROC. 2011. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Annals of Surgery* **253**: 431–441.

Bunn F, Roberts I, Tasker R, Akpa E. 2004. Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients. *The Cochrane Database of Systematic Reviews* **3**: CD002045.

Burchett H, Umoquit M, Dobrow M. 2011. How do we know when research from one setting can be useful in another? A review of external validity, applicability and transferability frameworks. *Journal of Health Services Research & Policy* **16**: 238–244.

Caldwell FT, Bowser BH. 1979. Critical evaluation of hypertonic and hypotonic solutions to resuscitate severely burned children: a prospective study. *Annals of Surgery* **189**: 546–552.

Cofield SS, Conwit R, Barsan W, Quinn J. 2010. Recruitment and retention of patients into emergency medicine clinical trials. *Academic Emergency Medicine* **17**: 1104–1112.

Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, Investigators HTSS. 2004. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *JAMA* **291**: 1350–1357.

Corbett MS, Higgins JPT, Woolacott NF. 2014. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Research Synthesis Methods* **5**: 79–85.

Dekkers OM, von Elm E, Algra A, Romijn JA, Vandenbroucke JP. 2010. How to assess the external validity of therapeutic trials: a conceptual approach. *International Journal of Epidemiology* **39**: 89–94.

Dutton RP, Mackenzie CF, Scalea TM. 2002. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. *Journal of Trauma* **52**: 1141–1146.

Evans PA, Garnett M, Boffard K, Kirkman E, Jacobson BF. 1996. Evaluation of the effect of colloid (Haemaccel) on the bleeding time in the trauma patient. *Journal of the Royal Society of Medicine* **89**: 101P–104P.

Gausche M, Lewis RJ, Stratton SJ, Haynes BE, Gunter CS, Goodrich SM, Poore PD, McCollough MD, Henderson DP, Pratt FD, Seidel JS. 2000. Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: a controlled clinical trial. *JAMA* **283**: 783–790.

Goldenberg IF, Campion BC, Siebold CM, McBride JW, Long LA. 1986. Esophageal gastric tube airway vs endotracheal tube in prehospital cardiopulmonary arrest. *Chest* **90**: 90–96.

Halliday HL, Sweet DG. 2001. Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No., CD000500. DOI: 10.1002/14651858.CD000500.

Herbison P. 2012. Guest blog by Peter Herbison: what should be done with quasi-randomised trials?. In Cochrane Editorial Unit. The Cochrane Collaboration.

Hypothermia After Cardiac Arrest Study (HACA). 2002. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *New England Journal of Medicine* **346**: 549–556.

James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. 2011. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *British Journal of Anaesthesia* **107**: 693–702.

Kwan I, Bunn F, Roberts I. 2003. Timing and volume of fluid administration for patients with bleeding. *Cochrane Database of Systematic Reviews* **3**: CD002245.

Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche JD, Ohanessian A, Spaulding C, Carli P, Dhainaut JF, Monchi M. 2005. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. *Journal of the American College of Cardiology* **46**: 432–437.

Lecky F, Bryden D, Little R, Tong N, Moulton C. 2008. Emergency intubation for acutely ill and injured patients. *Cochrane Database of Systematic Reviews* **2**: CD001429.

Linder N, Aranda J, Tsur M, Matoth I, Yatsiv I, Mandelberg H, Rottem M, Feigenbaum D, Ezra Y, Tamir I. 1988. Need for endotracheal intubation and suction in meconium-stained neonates. *The Journal of Pediatrics* **112**: 613–615.

Mattox KL, Maningas PA, Moore EE, Mateer JR, Marx JA, Aprahamian C, Burch JM, Pepe PE. 1991. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. The U.S.A. multicenter trial. *Annals of Surgery* **213**: 482–491.

Oransky I. 2013. What happened to Joachim Boldt's 88 papers that were supposed to be retracted?

Perel P, Roberts I. 2011. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews* **3**: CD000567.

Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. 2012. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database of Systematic Reviews* **8**: CD003248.

Rabitsch W, Schellongowski P, Staudinger T, Hofbauer R, Dufek V, Eder B, Raab H, Thell R, Schuster E, Frass M. 2003. Comparison of a conventional tracheal airway with the Combitube in an urban emergency medical services system run by physicians. *Resuscitation* **57**: 27–32.

Ramji S, Ahuja S, Thirupuram S, Rootwelt T, Rooth G, Saugstad OD. 1993. Resuscitation of asphyxic newborn infants with room air or 100% oxygen. *Pediatric Research* **34**: 809–812.

Ramji S, Rasaily R, Mishra PK, Narang A, Jayam S, Kapoor AN, Kambo I, Mathur A, Saxena NC, Saxena BN. 2003. Resuscitation of asphyxiated newborns with room air or 100% oxygen at birth: a multicentric clinical trial. *Indian Pediatrics* **40**: 510–517.

Saugstad OD, Ramji S, Soll RF, Vento M 2008. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. *Neonatology* **94**: 176–182.

Saugstad OD, Rootwelt T, Aalen O. 1998. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics* **102**: e1.

Toma A, Nanea M, Scheiner M, Mitu R, Petrescu I, Matu E. 2006a. Efectele gazului folosit pentru reanimarea non-nascutului asupra hemodinamicii post-resuscitare (articles in Romanian, abstract in English); in: Asfixia Perinatala. Primul Congress National de Neonatologie cu Participare Internationala, Cluj, 2006. *Medicala Universitara 'Iuliu Hatieganau'* 34–44.

Toma A, Sarbu A, Popescu O, Mitu A, Dobrescu M. 2006b. Room air versus oxygen in the resuscitation of term infants. *E-PAS* **59**: 2860–201.

Toma AI, Albu DF, Dambenau IM, Constantinescu A, Nanea M, Scheiner M, Vamescu B, Lancu M, Ghinea R. 2007. abstract. 21% versus 100% oxygen in the resuscitation of term infants. Prague *ESPR*.

Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D. 2000. A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. *Health Technology Assessment* **4**: 1–57.

Urbach P. 1993. The value of randomization and control in clinical trials. *Statistics in Medicine* **12**: 1421–31; discussion 1433-1441.

Vassar MJ, Fischer RP, O'brien PE, Bachulis BL, Chambers JA, Hoyt DB, Holcroft JW. 1993. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. The Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. *Archives of Surgery* **128**: 1003–11; discussion 1011-1013.

Vento M, Asensi M, Sastre J, Garcia-Sala F, Vina J. 2001. Six years of experience with the use of room air for the resuscitation of asphyxiated newly born term infants. *Biology of the Neonate* **79**: 261–267.

Vento M, Asensi M, Sastre J, Lloret A, Garcia-Sala F, Vina J. 2003. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. *The Journal of Pediatrics* **142**: 240–246.
Vento M, Sastre J, Asensi MA, Vina J. 2005. Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. *American Journal of Respiratory and Critical Care Medicine* **172**: 1393–1398.
Wiswell TE, Gannon CM, Jacob J, Goldsmith L, Szyld E, Weiss K, Schutzman D, Cleary GM, Filipov P, Kurlat I, Caballero CL, Abassi S, Sprague D, Oltorf C, Padula M. 2000. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. *Pediatrics* **105**: 1–7.
Wood L, Egger M, Gluud LL, Schulz K, Juni P, Altman DG, Gluud C, Martin RM, Wood AJG, Sterne J. 2008. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed)* **336**: 601–605.
Worrall J. 2002. What evidence in evidence-based medicine? *Philosophy of Science* **69**: S316–S330.
Zhao W, Ciolino J, Palesch Y. 2010. Step-forward randomization in multicenter emergency treatment clinical trials. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine* **17**: 659–665.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

Data extracted for individual trials, by review

Review: Room air or pure oxygen for newborns

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>
Trial reference and source review
(Bajaj et al., 2005), (Saugstad et al., 2008)

Country
India

Intervention and comparator
Room air versus 100% oxygen

Sequence generation method
Based on date of birth; even dates were resuscitated with 100% and odd dates were resuscitated with room air

Reason for using quasi-random method
‘To simplify enrolment as resuscitation is a medical emergency and delay could be detrimental to the babies’. (Also referenced other studies using quasi-random methods.)

Allocation concealment method
No allocation concealment

Type of consent obtained
Written informed consent, in accordance with the ethics committee, was obtained from the parents on admission to the hospital
</td>
<td>
Target sample size
At least 146

Number of recruiting centres
1

Recruitment period
April 2001 to June 2002 (15 months)

Number actually randomised
204

Number of patients randomised who did not receive the allocated treatment
None

Estimated monthly rate of randomisation
14

Number of ineligible patients randomised
None

Number of eligible patients not randomised (and a summary of the reasons)
None
</td>
<td>
Key eligibility criteria
Newborn weighing ≥1000g with apnoea or gasping respiration and/or heart rate <100 beats/min requiring positive pressure ventilation after the initial steps of resuscitation.

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
No important differences between groups

<table>
<tr><th>Characteristics</th><th>Room air (n=107)</th><th>100% oxygen (n=97)</th></tr>
<tr><td>Mean birth weight (g)</td><td>2461 (SD 602)</td><td>2319 (SD 614)</td></tr>
<tr><td>Gestational age (weeks)</td><td>38.3 (SD 2.8)</td><td>37.4 (SD 3.5)</td></tr>
<tr><td>Heart rate at birth (beats/min)</td><td>96 (SD 28)</td><td>100 (SD 28)</td></tr>
</table>

Notes
</td>
</tr>
</table>

General trial details	Recruitment	Population
Trial reference and source review (Ramji et al., 1993), (Saugstad et al., 2008) **Country** India **Intervention and comparator** Room Air versus 100% oxygen **Sequence generation method** Based on date of birth – even dates received room air, odd dates received 100% oxygen **Reason for using quasi-random method** NR **Allocation concealment method** No allocation concealment **Type of consent obtained** NR	**Target sample size** 72 **Number of recruiting centres** 1 **Recruitment period** NR **Number actually randomised** 84 **Number of patients randomised who did not receive the allocated treatment** 0 **Estimated monthly rate of randomisation** Unable to calculate **Number of ineligible patients randomised** 0 **Number of eligible patients not randomised (and a summary of the reasons)** One neonate in the room air group was apnoeic with a heart rate of zero and could not be resuscitated (and was declared a stillbirth).	**Key eligibility criteria** Asphyxiated new born weight >999g, heart rate <80 bpm and/or apnoea at birth **Key characteristics of population actually recruited (including all pre-specified prognostic indicators)** **Notes** 6 Neonates in the room air group who were cyanosed and/or bradycardic after 90 seconds were switched to 100% oxygen supplementation. But these neonates were retained in the room air group for statistical analysis (intention to treat). This study was also intended as a pilot study to calculate sample size requirements for later studies.

Characteristics	Room air (n=42)	100% oxygen (n=42)
Mean birth weight (g)	2,410 (SD 540)	2,410 (SD 660)
Gestational age (weeks)	38.4 (SD 1.9)	38.1 (SD 2.6)

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Ramji et al., 2003), (Saugstad et al., 2008)

Country
India

Intervention and comparator
Room Air versus 100% oxygen

Sequence generation method
Based on date of birth – even dates received room air, odd dates received 100% oxygen

Reason for using quasi-random method
To avoid practical difficulties in using random slips which may have caused a delay in institution of emergency therapy

Allocation concealment method
No allocation concealment

Type of consent obtained
Informed consent was obtained from parents at the time of admission</td>
<td>Target sample size
300

Number of recruiting centres
4

Recruitment period
1995 to 1997 (estimated as 24 months per centre)

Number actually randomised
433

Estimated monthly rate of randomisation (per centre)
4

Number of ineligible patients randomised
2 (congenital malformations)

Number of eligible patients not randomised (and a summary of the reasons)
0</td>
<td>Key eligibility criteria
New born >1000g, heart beat <100/bpm, apnoeic, unresponsive to nasopharyngeal suction and tactile stimuli

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table>
<tr><th>Characteristics</th><th>Room air (n=204)</th><th>100% oxygen (n=214)</th></tr>
<tr><td>Mean birth weight (g)</td><td>2,399 (SD 564)</td><td>2,508 (SD 638)</td></tr>
<tr><td>Gestational age (weeks)</td><td>37.9 (SD 2.9)</td><td>38.1 (SD 2.7)</td></tr>
</table>
Notes
Some of the infants enrolled in an earlier study(Saugstad et al., 1998) were later reported in this study. The review author corrected the characteristics data so that no infants were reported more than once.(Saugstad et al., 2008)</td>
</tr>
</table>

General trial details	Recruitment	Population
Trial reference and source review (Saugstad et al., 1998), (Saugstad et al., 2008) **Country** India, Egypt, Phillipines, Estonia, Spain, Norway **Intervention and comparator** Room air versus 100% oxygen **Primary outcome** Death within one week, and/or presence of grade II or III hypoxic ischaemic encephalopathy **Sequence generation method** Based on date of birth - even dates received room air, odd dates received 100% oxygen. **Reason for using quasi-random method** Concern that formal randomisation could have resulted in a delay in treatment, and a reduction in recruitment, especially for the most depressed infants, possibly leading to a non-representative sample. **Allocation concealment method** No allocation concealment **Type of consent obtained** No informed consent before enrolment. After treatment, informed consent for continued inclusion sought from	**Target sample size** 648 **Number of recruiting centres** 11 **Recruitment period** June 1994 to May 1996 (24 months) **Number actually randomised** 703 **Number of patients randomised who did not receive the allocated treatment** 16 infants allocated to the wrong group **Estimated monthly rate of randomisation** 3 (per centre) **Number of ineligible patients randomised** 90 **Number of eligible patients not randomised (and a summary of the reasons)** 107: In some cases the study team arrived after resuscitation had started, in other cases obstetricians did not want to enrol the infant.	**Key eligibility criteria** Newborn infants with apnoea or gasping with heart rate <80 bpm at birth. Weight>1000g. **Key characteristics of population actually recruited (including all pre-specified prognostic indicators)** No important differences between groups **Notes** The 86 ineligible infants all came from the same centre. All 94 infants recruited by this centre were excluded by the steering committee. The 16 infants give the wrong treatment were analysed according to the treatment they actually received. None of the 33 infants recruited from the 3 European centres died.

Characteristic	Room air (n=280)	100% oxygen (n=311)
Mean birth weight (g)	2,634 (SD 826)	2,608 (SD 312)
Gestational age (weeks)	37.6 (SD 3.0)	37.7 (SD 3.0)

parents. 36 parents opted out of further follow up.		

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Toma et al., 2006a), (Saugstad et al., 2008)

Country
Romania

Intervention and comparator
Room air versus 100% oxygen

Sequence generation method
Computer generated

Allocation concealment method
NR

Type of consent obtained
NR</td>
<td>Target sample size
NR

Number of recruiting centres
2

Recruitment period
NR

Number actually randomised
54

Number of patients randomised who did not receive the allocated treatment
NR

Estimated monthly rate of randomisation
NR

Number of ineligible patients randomised
NR

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Term infants who need resuscitation at birth, Heart rate<100 bpm, apnoea.

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>Room air (n=27)</th><th>100% oxygen (n=27)</th></tr>
<tr><td>Mean birth weight (g)</td><td>3536 (SD 519)</td><td>3530 (SD 337)</td></tr>
<tr><td>Gestational age (weeks)</td><td>39.1 (1.0)</td><td>39.2 (0.7)</td></tr>
</table>

Notes</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Toma et al., 2006b), (Saugstad et al., 2008)

Country
Romania

Intervention and comparator
Room air versus 100% oxygen

Sequence generation method
Computer generated

Allocation concealment method
NR

Type of consent obtained
NR</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
1.5.2006 to 1.8.2006 (3mths)

Number actually randomised
44

Number of patients randomised who did not receive the allocated treatment
NR

Estimated monthly rate of randomisation
14.6

Number of ineligible patients randomised
NR

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Newborn infants (≥34 weeks gestational age) who need resuscitation at birth, Heart rate<100 bpm, apnoea.

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>Room air (n=20)</th><th>100% oxygen (n=24)</th></tr>
<tr><td>Mean birth weight (g)</td><td>2684 (SD 1013)</td><td>2468 (SD 685)</td></tr>
<tr><td>Gestational age (weeks)</td><td>36.0 (SD 2.7)</td><td>35.3 (SD 2.2)</td></tr>
</table>

Notes
None</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Toma et al., 2007, abstract), (Saugstad et al., 2008)

Country
Romania

Intervention and comparator
Room air versus 100% oxygen

Sequence generation method
Computer generated

Allocation concealment method
NR

Type of consent obtained
NR</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
NR

Number actually randomised
56

Number of patients randomised who did not receive the allocated treatment
NR

Estimated monthly rate of randomisation
NR

Number of ineligible patients randomised
NR

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Term infants who need resuscitation at birth, heart rate<100 bpm, apnoea.

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>Room air (n=30)</th><th>100% oxygen (n=26)</th></tr>
<tr><td>Mean birth weight (g)</td><td>3172 (SD 599)</td><td>3200 (SD 200)</td></tr>
<tr><td>Gestational age (weeks)</td><td>38.8 (SD 0.78)</td><td>38.6 (SD 0.58)</td></tr>
</table>

Notes</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Vento et al., 2001), (Saugstad et al., 2008)

Country
Spain

Intervention and comparator
Room air versus 100% oxygen

Sequence generation method
Aleatoric numbers used

Allocation concealment method
Numbers used in a sequential manner.
Unclear risk

Type of consent obtained
Informed consent obtained from parents when mother was admitted to ward (before delivery)</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
6 years (1994 to 1999 - 72 months)*

Number actually randomised
527**

Number of patients randomised who did not receive the allocated treatment
NR

Estimated monthly rate of randomisation
Not possible to calculate a viable estimate

Number of ineligible patients randomised
NR

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Term infants (37-42 weeks gestatitional age), Heart rate<80 bpm, apnoea, pH <7.05, temperature <37.5 C

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table>
<tr><th>Characteristics</th><th>Room air (n=300)</th><th>100% oxygen (n=237)</th></tr>
<tr><td>Mean birth weight (g)</td><td>3,380 (SD 318)</td><td>3,190 (SD 245)</td></tr>
<tr><td>Gestational age (weeks)</td><td>38.6 (SD 1.7)</td><td>40.2 (SD 0.8)</td></tr>
</table>

Notes
*This paper is a summary of this hospital’s previous randomised trials.

Details of randomisation and eligibility criteria were extracted from the systematic review.(Saugstad et al., 2008)

**Some of the infants enrolled in an earlier study(Saugstad et al., 1998) were later reported in this study. The review author corrected the characteristics data so that no infants were reported more than once.(Saugstad et al., 2008) It is unclear though why there is such a large imbalance in the number of randomised infants.</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Vento et al., 2003), (Saugstad et al., 2008)

Country
Spain

Intervention and comparator
Room Air versus 100% oxygen

Sequence generation method
Computer generated random number

Allocation concealment method
‘Sealed envelope’ assigned to each mother’s record on admission (before delivery). A nurse opened the envelope and switched the gas source accordingly.
Unclear risk of bias.

Type of consent obtained
Informed parental consent was obtained on admission before the delivery</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
NR

Number actually randomised
151

Estimated monthly rate of randomisation
Unable to calculate

Number of ineligible patients randomised
biochemical requirements (n = 10), having insufficient blood for analytical purposes (n = 14),

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Term asphyxiated infants (37 to 40 weeks gestation), heart rate <80bpm, apnoea, PH≤7.05, temperature <37.5 C

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table>
<tr><th>Characteristics</th><th>Room air (n=51)</th><th>100% oxygen (n=55)</th></tr>
<tr><td>Mean birth weight (g)</td><td>3,160 (SD 240)</td><td>3,220 (SD 168)</td></tr>
<tr><td>Gestational age (weeks)</td><td>38.9 (SD 1.6)</td><td>40.5 (SD 1.1)</td></tr>
<tr><td>Fetal bradycardia at birth (< 80 bpm)</td><td>34</td><td>32</td></tr>
</table>
Notes
45 neonates were excluded, because of not fulfilling the biochemical requirements (n = 10), having insufficient blood for analytical purposes (n = 14), because they were switched from room air to 100% oxygen (n = 7) or vice-versa (n = 5), or because they were not blindly resuscitated (n = 9)

The authors used another control group n=22 (Infants for the control group were selected from among nonasphyxiated term neonates)</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Vento et al., 2005), (Saugstad et al., 2008)

Country
Spain

Intervention and comparator
Room Air versus 100% oxygen

Sequence generation method
A random number was assigned to each record which stated whether room air or 100% oxygen was used.

Allocation concealment method
NR

Type of consent obtained
Informed parental consent was obtained on admission before the delivery</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
Four year period (1999 to 2002 - 48 months)

Number actually randomised
Appeared to be 53

Number of patients randomised who did not receive the allocated treatment
9:
4 infants received a change in gas mixture (when ventilation proved unsuccessful). 5 needed supplemental oxygen.

Estimated monthly rate of randomisation
1

Number of ineligible patients randomised
Not totally clear, though 3 infants were ‘improperly randomised’.

Number of eligible patients not randomised (and a summary of the reasons)
None</td>
<td>Key eligibility criteria
Severely asphyxiated neonates (gestational age 37-42 wks, bradycardia (<80 beats/min), non-responsiveness to stimuli, a cord pH of 7.0 or less at birth, and an Apgar score of 5 or less for more than 5 min)

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>Room air (n=17)</th><th>100% oxygen (n=22)</th></tr>
<tr><td>Mean birth weight (g)</td><td>3,320 (SD 180)</td><td>3,110 (SD 90)</td></tr>
<tr><td>Gestational age (weeks)</td><td>39.6 (SD 1.6)</td><td>39.2 (SD 1.1)</td></tr>
<tr><td>Foetal bradycardia at birth (< 80 bpm)</td><td>11</td><td>14</td></tr>
</table>

Notes
The authors also used a non-randomised control group n=22 (selected from among non-asphyxiated term neonates who were born on the same day as asphyxiated infants included in the trial).</td>
</tr>
</table>

Review: Endotracheal intubation for neonates

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Linder et al., 1988), (Halliday and Sweet, 2001)

Country
Unclear (Israel or Canada)

Intervention and comparator
Intubation plus suction (aspirated) vs no intubation plus suction (not aspirated)

Sequence generation method
Paediatricians were randomised based on the alphabetical order of their names.

Reason for using quasi-random method
None given

Type of consent obtained
Obtained only from the parents whose babies were not suctioned</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
June 1984 to December 1986: 31 months

Number actually randomised
572

Estimated monthly rate of randomisation, per centre
18

Number of ineligible patients randomised
None

Number of eligible patients not randomised (and a summary of the reasons)
None</td>
<td>Key eligibility criteria
Gestational age >37 weeks, birth weight >2500g, 1-minute Apgar score>8

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table>
<tr><th>Characteristics</th><th>Aspirated (n=308)</th><th>Not aspirated (n=264)</th></tr>
<tr><td>Weight (g)</td><td>3300 (SD 435)</td><td>3420 (SD 319)</td></tr>
<tr><td>Age (weeks)</td><td>39.8 (SD 1.1)</td><td>39.6 (SD 1.4)</td></tr>
</table>
Notes
Babies aspirated by non-participating paediatricians were included in the aspirated group.</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Wiswell et al., 2000), (Halliday and Sweet, 2001)

Country
USA

Intervention and comparator
Intubation and intratracheal suctioning vs expectant management

Sequence generation method
Computer-generated random numbers

Allocation concealment method
Sealed opaque envelopes were drawn but envelopes were opened immediately before deliveries.

Type of consent obtained
No consent obtained (the protocol satisfied the requirements for a waiver (as outlined in Federal Regulations)</td>
<td>Target sample size
2058

Number of recruiting centres
12

Recruitment period
27 months (July 1995 to September 1997)

Number actually randomised
2094

Estimated monthly rate of randomisation, per centre
6

Number of ineligible patients randomised
Unclear. Envelopes were opened immediately before deliveries; when infants did not meet the vigour criteria they were excluded from the study and the randomisation assignment discarded.

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Gestational age ≥ 37 weeks, meconium stained amniotic fluid, apparent vigour immediately after birth (such as heart rate >100bpm), as well as presence of spontaneous movements or had some degree of extremity flexion

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table><tr><th>Characteristics</th><th>Intubate (n=1051)</th><th>Expectant (n=1043)</th></tr><tr><td>Gestational age</td><td>NR</td><td>NR</td></tr><tr><td>Heart rate</td><td>NR</td><td>NR</td></tr></table>
Notes
Six of the 12 sites enrolled a cumulative total of 227 of the 2094 infants.

17 infants did not receive intubation, due to intubation difficulties
64 infants from Expectant group were intubated after the initial assessment period
No consent was sought in order to recruit a representative sample</td>
</tr>
</table>

Review: Colloids vs crystalloids for fluid resuscitation

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Bulger et al., 2011), (Perel and Roberts, 2011)

Country
US and Canada

Intervention and comparator
Hypertonic saline/dextran(HSD) vs hypertonic saline (HS) vs normal saline (NS)

Sequence generation method
Randomly generated numeric code labels generated (for use at single distribution centre). Ratio of 1:1:1.4 was used (for HS, HSD, and NS respectively).

Allocation concealment method
Code labels attached to identical intravenous bags. Patients were allocated a blinded bag of study fluid.

Type of consent obtained
Exception from informed consent regulations used. Consent was sought for continued follow up after arrival at hospital.</td>
<td>Target sample size
3726

Number of recruiting centres
114

Recruitment period
May 2006 to August 2008 (28 months)

Number actually randomised
895

Estimated monthly rate of randomisation, per centre
0.28

Number of ineligible patients randomised
23

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Age≥15 with hypovolemic shock (out of hospital systolic blood pressure ≤70 mmHg or 71-90mmHg with heart rate ≥108 bpm)

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table>
<tr><th>Characteristics</th><th>HSD (n=220)</th><th>HS (n=256)</th><th>NS (n=376)</th></tr>
<tr><td>Age (mean, SD)</td><td>37.7 (17.3)</td><td>36.8 (16.1)</td><td>36.2 (16.4)</td></tr>
<tr><td>TRISS probability (SD)</td><td>0.71 (0.32)</td><td>0.68 (0.35)</td><td>0.70 (0.32)</td></tr>
<tr><td>ISS (mean, SD)</td><td>22.8 (16.9)</td><td>24.2 (17.3)</td><td>23.9 (15.1)</td></tr>
<tr><td>Systolic blood pressure mmHg (mean, SD)</td><td>59.1 (35.5)</td><td>54.1 (35.3)</td><td>58.1 (32.2)</td></tr>
<tr><td>Qualifying HR (beats/min), mean (SD)</td><td>123.9 (18.1)</td><td>121.0 (17.6)</td><td>120.2 (18.3)</td></tr>
<tr><td>Out-of-hospital GCS, mean (SD)</td><td>10.0 (4.9)</td><td>10.0 (5.0)</td><td>9.8 (5.0)</td></tr>
</table>
Notes
*Data and safety monitoring board stopped the study early (at 23% of proposed sample size) based on results of a pre-specified safety subgroup analysis of survival.</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Evans et al., 1996), (Perel and Roberts, 2011)

Country
South Africa

Intervention and comparator
Colloid (Haemaccel) versus Crystalloid (Ringer’s lactate)

Sequence generation method
Allocation by day of week*

Reason for using quasi-random method
NR

Allocation concealment method
None

Type of consent obtained
NR</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
35 days(1month)

Number actually randomised
25

Estimated monthly rate of randomisation, per centre
25

Number of ineligible patients randomised
0

Number of eligible patients not randomised (and a summary of the reasons)
0 (though not totally clear)</td>
<td>Key eligibility criteria
Age>16yrs with blunt or penetrating trauma who needs intravenous fluid resuscitation, arrival at trauma unit within 2h of injury, Crystalloid (Ringer's lactate) as the only pre-hospital Infusion, no underlying illness or medication which would affect the patient's coagulating system

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table>
<tr><th>Characteristics</th><th>Colloid(n=11)</th><th>Crystalloid (n=14)</th></tr>
<tr><td>Median Age yr (IQR)</td><td>30(29-38)</td><td>30(25-39)</td></tr>
<tr><td>Median ISS (IQR)</td><td>25(16-34)</td><td>25(14-36)</td></tr>
<tr><td>Median RTS (IQR)</td><td>7.5(4.9-7.8)</td><td>6.3(4.4-7.8)</td></tr>
</table>
Notes</td>
</tr>
</table>

* Information obtained only from Cochrane review NA= not applicable, ISS injuries severity score, RTS revised trauma scores

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(James et al., 2011), (Perel and Roberts, 2011)

Country
South Africa

Intervention and comparator
Hydroxyethyl starch (HES) versus Saline

Sequence generation method
Random numbers grouped in blocks of 8 for each category of trauma (penetrating or blunt) in a ratio of 1:1 for the study fluid.

Allocation concealment method
Identical 500ml bags were sealed in black plastic to conceal the label and contents and packed in numbered, sequentially-ordered boxes by the pharmacist.

Type of consent obtained
Deferred written informed consent was obtained from participants or their legally acceptable representatives</td>
<td>Target sample size
140

Number of recruiting centres
1

Recruitment period
3 years

Number actually randomised
115

Estimated monthly rate of randomisation, per centre
3

Number of ineligible patients randomised
5(two under age, prior colloids, too old or severe head injury, unresponsive blood pressure(BP))

Number of eligible patients not randomised (and a summary of the reasons)
0</td>
<td>Key eligibility criteria
Age between 18 to 60 years with penetrating or blunt trauma patients who required >3 litre volume resuscitation

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>P-HES (n=36)</th><th>P-SAL (n=31)</th><th>B-HES (n=20)</th><th>B- SAL (n=22)</th></tr>
<tr><td>Age yr, mean(range)</td><td>27.6(18-49)</td><td>32.6(21-56)</td><td>33(18-50)</td><td>35.7(20-58)</td></tr>
<tr><td>ISS, median (range)</td><td>18(9-45)</td><td>16(8-34)</td><td>29.5(9-57)*</td><td>18(9-66)</td></tr>
<tr><td>NISS median (range)</td><td>34(10-57)</td><td>27(10-66)</td><td>36(22-66)*</td><td>27(13-66)</td></tr>
</table>

Notes
Penetrating and blunt trauma patients were randomised separately, with data analysed independently.

The study was stopped after 3 years because of a change in referral patterns leading to a decline in patient numbers.

One patient received ‘both boxes’(protocol violation)</td>
</tr>
</table>

Penetrating HES (P-HES), Penetrating Saline (P-SAL), Blunt HES (B-HES), Blunt Saline (B-SAL), injury severity score (ISS), new injury severity score (NISS)

Review: Timing and volume of fluid administration

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>
Trial reference and source review
(Bickell et al., 1994), (Kwan et al., 2003)

Country
USA

Intervention and comparator
Immediate versus delayed fluid resuscitation

Sequence generation method
Immediate group were enrolled on even-numbered days of the month

Delayed group were enrolled on odd-numbered days of the month

Reason for using quasi-random method
Due to the nature of the study (to avoid the detrimental delay in care for critically injured patients) formal randomisation procedure were considered not to be logistically feasible

Allocation concealment method
None

Type of consent obtained
A policy of waived consent which adhered to the principle of implied consent was approved by the
</td>
<td>
Target sample size
Approximately 600

Number of recruiting centres
1

Recruitment period
37 months

Number actually randomised
598

Estimated monthly rate of randomisation, per centre
16

Number of ineligible patients randomised
See notes

Number of eligible patients not randomised (and a summary of the reasons)
0
</td>
<td>
Key eligibility criteria
age≥16yrs with gunshot or stab wounds to the torso who had SBP ≤ 90mmHg,including patients with no measurable BP, at the time of the scene

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)
<table>
<tr><th>Characteristics</th><th>Immediate(n=309)</th><th>Delayed(n=289)</th></tr>
<tr><td>Age (yr)</td><td>31 (SD 11)</td><td>31 (SD 10)</td></tr>
<tr><td>SBP (mmHg)</td><td>58 (SD 35)</td><td>59 (SD 34)</td></tr>
<tr><td>Injury severity score</td><td>26 (SD 14)</td><td>26 (SD14)</td></tr>
<tr><td>Revised trauma score</td><td>5.4 (SD 2.1)</td><td>5.6 (SD 2.1)</td></tr>
<tr><td>Probability of survival</td><td>69</td><td>72</td></tr>
</table>
Notes
Of the 1069 eligible patients, 471 were ineligible for the final study analysis (172 had revised trauma score of zero on initial evaluation, 299 patients were found to have minor injuries that did not require surgery). This analysis plan was part of the prospective study design; paramedics caring for patients were not made aware of these exclusion criteria.
</td>
</tr>
</table>

institutional review board		

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Dutton et al., 2002), (Kwan et al., 2003)

Country
USA

Intervention and comparator
Fluid administration titrated to a ‘conventional’ systolic blood pressure(SBP) >100mmHg or to a ‘low’ SBP of 70 mmHg

Sequence generation method
Thoroughly mixed envelopes*

Allocation concealment method
Thoroughly mixed but then sequentially numbered envelopes (batches of 20). Allocation blinded to all unit personnel.*

Type of consent obtained
Delayed consent was used - informed consent was obtained from patients or their guardians as soon as possible after study enrollment</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
1996 to 1999 – the authors also stated that patients were enrolled over a period of 20 months

Number actually randomised
110

Estimated monthly rate of randomisation, per centre
6 (based on 20 months)

Number of ineligible patients randomised
NR

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Had to be presented directly from the scene of a traumatic injury, evidence of ongoing haemorrhage, had an SBP <90mmHg recorded at least once within the first hour of injury

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>SBP>100mmHg (n=55)</th><th>SBP=70mmHg (n=55)</th></tr>
<tr><td>Average age (yr)</td><td>29.7 (SD 13.0)</td><td>32.1 (SD10.5)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Probability of survival (TRISS)</td><td>94.0% (12)</td><td>90.2% (17)</td></tr>
<tr><td>ISS</td><td>19.6 (11.6)</td><td>23.9 (13.8)</td></tr>
</table>

Notes</td>
</tr>
</table>

*Details obtained from the systematic review (not stated in trial report)

General trial details	Recruitment	Population
Trial reference and source review (Turner et al., 2000), (Kwan et al., 2003) **Country** UK **Intervention and comparator** Early (protocol A) versus no or delayed (protocol B) infusion of intravenous fluids **Sequence generation method** Paramedic, rather than patients, were randomised to one of the two treatment protocols. Computer generated randomisation. Randomisation was stratified by base ambulance station (34 in area 1 and 11 in area 2). Paramedics were listed by station and sequentially assigned a treatment protocol from the random number string for that station. Total of 311 paramedics, 237 in area 1 and 74 in area 2 were randomised, with an additional 90 paramedics added during the study (72 in area 1 and 18 in area 2), giving a total of 401 paramedics in all. A total of 54 British Association of Immediate Care Schemes (BASICS)	**Target sample size** NA **Number of recruiting centres** 17 **Recruitment period** May 1996 to September 1997 (17months) **Number actually randomised** 1309 patients **Estimated monthly rate of randomisation, per centre** 5 patients per centre **Number of ineligible patients randomised** None **Number of eligible patients not randomised (and a summary of the reasons)** None	**Key eligibility criteria** Trauma patients (moderate to severely injured) aged 16 years or over attended by a paramedic crew or BASICS doctors randomised to a treatment protocol and who died or stayed in hospital for three or more nights **Key characteristics of population actually recruited (including all pre-specified prognostic indicators)** Age and injury severity score details were provided using (numbers of patients in) categories. The groups appeared to be well-balanced. **Notes** Random allocation of a protocol to patients presented several difficulties. Firstly, there were issues around the requirement to obtain informed consent to randomisation from patients at the incident scene. For some patients for example those who were unconscious, this would not be possible. For others, even if awake and talking, the process of providing information and requesting consent from an injured person immediately after an accident seemed inappropriate. Furthermore, this process, if carried out properly, would inevitably lead to delays at the scene and would therefore be contrary to the basic prehospital care management principle of transporting the patient to hospital as quickly as possible. It is possible to waive the requirement to obtain informed consent in certain emergency situations and critical patient conditions. However, it was envisaged that the patient group eligible for inclusion in this trial was likely to be sufficiently heterogeneous with respect to injury type and physiological condition at the incident scene that the waiver conditions would not apply in every case. This could lead to difficulties for the attending paramedics, as they would be required to decide whether or not informed consent should be sought. The advantage of randomising paramedics was that there

doctors were also randomised to protocols A or B. Both paramedics and doctors switched protocols half way through the trial. **Allocation concealment method** None **Type of consent obtained** Did not need consent as paramedics, rather than patients, were randomised. Patient consent was not requested at the incident scene, patients were informed of the trial after the incident.		was no requirement for consent to be obtained prior to giving treatment, as no choice was involved. The disadvantage was that this method resulted in no allocation concealment.

Review: Hypertonic versus near isotonic crystalloids for fluid resuscitation in critically ill patients

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Caldwell and Bowser, 1979), (Bunn et al., 2004)

Country
USA

Intervention and comparator
Hypertonic lactated saline(HLS) versus lactated Ringer's solution (LRS)

Sequence generation method
Treatments were alternated

Reason for using quasi-random method
NR

Type of consent obtained
NR</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
July 1975 and July 1978 (37 months)

Number actually randomised
37

Estimated monthly rate of randomisation, per centre
1

Number of ineligible patients randomised
NR

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Children with thermal burns covering 30% or more of the body surface area

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>LRS(n=20)</th><th>HLS(n=17)</th></tr>
<tr><td>Age yr, mean</td><td>7.4</td><td>9.5</td></tr>
<tr><td>Serum sodium (SD)</td><td>138(2.9) (n=17)</td><td>141(4.2) (n=17)</td></tr>
<tr><td>Serum potassium (SD)</td><td>4.0(0.5) (n=17)</td><td>4.0(0.5) (n=16)</td></tr>
<tr><td>Serum osmolality (SD)</td><td>288(12) (n=12)</td><td>295(6) (n=16)</td></tr>
<tr><td>Hematocrit (SD)</td><td>43(5) (n=18)</td><td>46(8) (n=16)</td></tr>
</table>

Notes</td>
</tr>
</table>

General trial details

Trial reference and source review
(Cooper et al., 2004), (Bunn et al., 2004)

Country
Australia

Intervention and comparator
hypertonic saline (HTS) versus Ringer's lactate solution (control)

Sequence generation method
Computer-randomisation

Allocation concealment method
The colourless study fluids were contained in identical bags which were used according to their sequence number. Bags were packed in blocks of 4 into each ambulance

Type of consent obtained
Pre-hospital informed consent was waived. Delayed written consent for participation and continuation in the study was
obtained from the next of kin or patients if they recovered

Recruitment

Target sample size
220

Number of recruiting centres
12

Recruitment period
December 14, 1998, and April 9, 2002 (41months)

Number actually randomised
229

Estimated monthly rate of randomisation, per centre
0.5

Number of ineligible patients randomised
0

Number of eligible patients not randomised (and a summary of the reasons)
0

Population

Key eligibility criteria
Adults with blunt traumatic brain injury who were comatose (Glasgow Coma Scale score <9) and hypotensive (systolic blood pressure <100 mm Hg). Patients with multiple system trauma were also included.

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

Characteristics	HTS (n=114)	Control(n=115)
Age mean (SD) , yr	38 (19)	37 (19)
Systolic blood pressure, median (IQR), mm Hg	80 (38-90)	70 (0-85)
Glasgow Coma Scale score, median (IQR)	4 (3-7)	4 (3-7)
Injury severity score, median (IQR)	38 (28-48)	38 (29-45)
TRISS at the trauma scene, median (IQR)	27 (10-66)	24 (6.4-59)
New injury severity score, median (IQR)	48 (41-57)	50 (41-66)
Maximum abbreviated injury score, median (IQR)	5 (4-5)	5 (4-5)
Head-abbreviated injury score,median (IQR)	4 (4-5)	4 (3-5)

Notes

General trial details	Recruitment	Population
Trial reference and source review (Vassar et al., 1993), (Bunn et al., 2004) **Country** USA **Intervention and comparator** Lactated Ringer's (LR) versus 7.5% sodium chloride (hypertonic saline solution [HS]) versus 7.5% sodium chloride combined with 6% dextran 70 (HSD-6%) versus 7.5% sodium chloride combined with dextran 70 (HSD-12%) **Sequence generation method** Computer generated random numbers, treatment group assignments were made in blocks of eight, two bags each for the four solutions. **Allocation concealment method** Bags were ordered sequentially and were indistinguishable from one another except for a coded identification tag **Type of consent obtained** Research review board waived informed consent	**Target sample size** 600 **Number of recruiting centres** 6 **Recruitment period** March 1990 to June 1991 (16 months) **Number actually randomised** 233 **Estimated monthly rate of randomisation, per centre** 2 **Number of ineligible patients randomised** 39 (patient undergoing cardiopulmonary resuscitation, systolic blood pressure ≥90mmHg when infusion started, >2h from injury when infusion started, vital signs when infusion started not recorded, <200ml of test solution administered **Number of eligible patients not randomised (and a summary of the reasons)** 0	**Key eligibility criteria** Injured patients > 18 years with systolic blood pressure <90 mmHg at any time in the filed or during helicopter transport, <2hrs from the time of injury. Patients with asystole or needed cardiopulmonary resuscitation were excluded. **Key characteristics of population actually recruited (including all pre-specified prognostic indicators)**

Characteristics	LR(n=45)	HS(n=50)	HSD-6%(n=50)	HSD-12% (n=49)
Age yr, mean (SD)	37(18)	31(13)	30(12)	34(15)
Predicted survival rate using TRISS (%)	47	48	52	40
Weighted revised trauma score, mean (SD)	4.3(2.3)	3.8(2.5)	4(2.4)	3.7(2.1)
Injury severity score, mean (SD)	33(19)	32(17)	32(22)	36(19)
No(%) with severe brain injury	15(33)	18(36)	14(28)	23(47)
Time from injury to arrive of helicopter, min , mean (SD)	41(18)	35(16)	37(17)	37(21)
Time from injury to start of infusion of test solution, min,	62(27)	51(22)	54(23)	54(25)

		mean (SD)				
		Time from infusion to test solution to ED arrival, min, mean (SD)	21(13)	17(13)	18(12)	19(10)
		Isotonic fluids given before infusion of test solution, L	1.3(1.2)	1.2(1.1)	1.3(1.1)	1.2(1.2)
		Glasgow coma scale (GCS) before infusion of test solution	9(6)	8(5)	9(5)	8(5)
		GCS on arrival in ED	9(6)	8(5)	9(5)	8(5)
		Systolic blood pressure for entire cohort before infusion mmHg	72(15)	66(27)	62(34)	65(22)
		Notes The trial did not reach the target sample due to the pharmaceutical closed the plant which had been manufacturing the solutions				

Review: Hypothermia for neuroprotection after cardiopulmonary resuscitation

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Bernard et al., 2002), (Arrich et al., 2009)

Country
Australia

Intervention and comparator
Hypothermia versus Normothermia

Sequence generation method
According to the day of the month; Hypothermia (odd-numbered days), Normothermia (even-numbered days)

Reason for using quasi-random method
It was the only one feasible for immediate use by large numbers of ambulance officers and by the physicians in four emergency departments

Type of consent obtained
Written informed consent for participation in the study was sought from the next of kin as soon as possible after the arrival of the patient at the hospital.</td>
<td>Target sample size
62

Number of recruiting centres
4

Recruitment period
September 1996 to June 1999 (33 months)

Number actually randomised
84

Estimated monthly rate of randomisation, per centre
0.6

Number of ineligible patients randomised
0

Number of eligible patients not randomised (and a summary of the reasons)
0</td>
<td>Key eligibility criteria
Patients >18yrs(men) and >50yrs (women) with cardiac arrest, an initial cardiac rhythm of ventricular fibrillation at the time of arrival of the ambulance, successful return of spontaneous circulation, persistent coma after the return of spontaneous circulation, and transfer to one of four participating emergency departments

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>Hypothermia (n=43)</th><th>Normothermia (n=34)</th></tr>
<tr><td>Age (median)</td><td>66.8</td><td>65.0</td></tr>
<tr><td>Male (%)</td><td>58</td><td>79</td></tr>
<tr><td>Bystander performed cardiopulmonary resuscitation (%)</td><td>49</td><td>71</td></tr>
<tr><td>Time from collapse to emergency medical services call (min)</td><td>2.1 (1.9)</td><td>2.7(3.0)</td></tr>
<tr><td>Time from arrival to first direct current shock (min)</td><td>2.5 (2.2)</td><td>2.0 (1.2)</td></tr>
<tr><td>Time from collapse to return of spontaneous circulation (min)</td><td>26.5 (12.9)</td><td>25.0 (8.9)</td></tr>
<tr><td>Mean arterial blood pressure (mm Hg)</td><td>90.4 (18.89)</td><td>87.2 (21.46)</td></tr>
<tr><td>Pulse (per minute)</td><td>97 (22.5)</td><td>105 (30.4)</td></tr>
</table>

Notes
Age (2 year difference) and time from collapse to return of spontaneous circulation (1.5 minute difference) were found to be important prognostic indicators.</td>
</tr>
</table>

		Treatment assignment was not blinded, and there is the possibility that some aspects of care differed between the groups.

General trial details	Recruitment	Population
Trial reference and source review (Hypothermia after Cardiac Arrest Study, 2002), (Arrich et al., 2009) **Country** Several European countries **Intervention and comparator** Normothermia versus hypothermia (32C to 34 C) **Sequence generation method** Randomly generated by computer in blocks of 10, with stratification according to centre. **Allocation concealment method** Sealed envelopes provided by biostatistics centre **Type of consent obtained** Informed consent was waived in accordance with the ethical standards of the local institutional review board and the guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal Products	**Target sample size** NR **Number of recruiting centres** 9 (in appendix) **Recruitment period** March 1996 to July 2000 (53 months) **Number actually randomised** 275 **Estimated monthly rate of randomisation, per centre** 0.6 **Number of ineligible patients randomised** 0 **Number of eligible patients not randomised (and a summary of the reasons)** 30 due to 'logistic problems'	**Key eligibility criteria** Patients who had a witnessed cardiac arrest, ventricular fibrillation or non perfusing ventricular tachycardia as the initial cardiac rhythm, a presumed cardiac origin of the arrest, an age of 18 to 75 years, an estimated interval of 5 to 15 minutes from the patient's collapse to the first attempt at resuscitation by emergency medical personnel, and an interval of no more than 60 minutes from collapse to restoration of spontaneous circulation. **Key characteristics of population actually recruited (including all pre-specified prognostic indicators)**

Characteristics	NORMOTHERMIA (n=138)	HYPOTHERMIA (n=137)
Age, yr (Median)	59	59
Diabetes (%)	19	8
Coronary heart disease (%)	43	32
Cerebrovascular disease (%)	8	7
NYHA class III or IV (%)	12	11
Basic life support provided by bystanders (%)	49	43
Interval between collapse and restoration of spontaneous circulation, min,(median)¶	22	21
Hypotension after resuscitation (%)	49	55
Subsequent non-fatal arrest (%)	8	11

		§Although this was a criterion for inclusion in the study, in a few cases, the initial information was incorrect. ¶ Data were not available for three patients in the normothermia group and four in the hypothermia group. †NYHA denotes New York Heart Association **Notes** Hypotension was noted as a risk factor for an unfavourable outcome. Personnel involved in the care of patients during the first 48 hours after cardiac arrest could not be blinded with respect to treatment assignments but the physicians responsible for assessing the neurologic outcome within the first six months after the arrest were blinded.

General trial details	Recruitment	Population
Trial reference and source review (Laurent et al., 2005), (Arrich et al., 2009) **Country** France **Intervention and comparator** Standard care (control) versus standard care plus either haemofiltration (HF) or HF+ mild hypothermia (HT) **Sequence generation method** Computer generated 1/1/1/ randomisation sequence **Allocation concealment method** Sealed opaque envelopes **Type of consent obtained** Informed written consent was obtained from the patients or their next- of- kin if they were comatose; however according to French Law treatment trials for immediate life-threatening situations, consent was not required to begin treatment.	**Target sample size** 90 **Number of recruiting centres** 2 **Recruitment period** May 2000 and March 2002 (23 months) **Number actually randomised** 61 **Estimated monthly rate of randomisation, per centre** 1 **Number of ineligible patients randomised** 0 **Number of eligible patients not randomised (and a summary of the reasons)** 0	**Key eligibility criteria** Patients age between 18 and 75yrs who had cardiac arrest related to heart disease, initial ventricular fibrillation or asystole, estimated interval of <10mins from cardiac arrest to initiation of cardiopulmonary resuscitation (no-flow interval), and interval of <50min from initiation of cardiopulmonary resuscitation to restoration of spontaneous circulation (low-flow interval) **Key characteristics of population actually recruited (including all pre-specified prognostic indicators)**

Characteristics	control(n=19)	HF(n=20)	HF+HT(n=22)
Age yrs (range)	58 (53-64)	52(47-59)	56(50-70)
History of CHD n (%)	2 (11)	6 (30)	3 (14)
Interval between collapse and first attempt at Resuscitation, min (range)	4 (2–8)	5 (2–10)	4(2–7)
Interval between first attempt at resuscitation and restoration of spontaneous circulation, min (range)	14(10-15)	25(10-38)	16(8-25)
Number of shocks (range)	3(1-5)	3(1-7)	3(1-4)
Hypotension requiring continuous adrenaline %	21	40	27

		Notes Blinding to the assigned treatment was not feasible The trial was stopped a year early because of the results found in other hypothermia trials. 45 minutes were needed to prime haemofiltration circuits

CHD=coronary heart disease

Review: Intubation for acutely ill and injured patients

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Gausche et al., 2000), (Lecky et al., 2008)

Country
USA

Intervention and comparator
Bag-valve-mask-ventilation (BVM) versus BVM followed by endotracheal intubation (ETI)

Sequence generation method
Day of month: BVM (odd days) versus
BVM followed by ETI (even days)

Reason for using quasi-random method
NR

Allocation concealment method
None

Type of consent obtained
Waiver of consent</td>
<td>Target sample size
800

Number of recruiting centres
Unclear

Recruitment period
March 15, 1994 to January 1, 1997 (approx. 34 months)

Number actually randomised
830

Estimated monthly rate of randomisation, per centre
Unclear

Number of ineligible patients randomised
None

Number of eligible patients not randomised (and a summary of the reasons)
The authors noted that paramedic knowledge of the forthcoming treatment might have influenced enrolment. Only one (possibly) missed subject was detected following an independent survey of emergency medical service records.</td>
<td>Key eligibility criteria
Out-of-hospital patients aged 12 years or younger or estimated to weigh less than 40kg who required airway management

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>BVM (n=403)</th><th>BVM+ETI(n=415)</th></tr>
<tr><td>Age (median, range)</td><td>1.2 (0 to 3.5)</td><td>1 (0.25 to 3.3)</td></tr>
<tr><td>Sex (% male)</td><td>61</td><td>57</td></tr>
<tr><td>Time to arrive on scene (mins, median)</td><td>5</td><td>5</td></tr>
<tr><td>Sudden infant death syndrome (%)</td><td>14</td><td>19</td></tr>
<tr><td>Submersion injury (%)</td><td>14</td><td>10</td></tr>
<tr><td>Head injury (%)</td><td>7</td><td>9</td></tr>
<tr><td>Multiple trauma (%)</td><td>9</td><td>12</td></tr>
<tr><td>Foreign body aspiration (%)</td><td>3</td><td>3</td></tr>
<tr><td>Status epilepticus (%)</td><td>9</td><td>8</td></tr>
<tr><td>Child maltreatment (%)</td><td>6</td><td>5</td></tr>
<tr><td>Cardiac arrest (%)</td><td>71</td><td>72</td></tr>
<tr><td>Respiratory arrest (%)</td><td>13</td><td>13</td></tr>
<tr><td>Reactive airway disease (%)</td><td>3</td><td>3</td></tr>
</table>
The proportion of children revieving cardiopulmonary resuscitation was equivalent between groups (information from Cochrane review).
Notes
There were 23 protocol violations : occurred 20 times on BVM days and 3 times on BVM+ETI days</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Goldenberg et al., 1986), (Lecky et al., 2008)

Country
USA

Intervention and comparator
Endotracheal tube (ET) versus Oesophageal gastric tube airway (EGTA)

Sequence generation method
A card which determined what intervention the patient would have received was drawn on paramedic arrival. The cards were placed in random order using a random numbers table.

Allocation concealment method
NR, though reasons for incorrect randomisation such as ‘looked at wrong card’ suggest that allocation concealment may not have been adequate.

Type of consent obtained
NR</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
24 months

Number actually randomised
175

Estimated monthly rate of randomisation, per centre
7

Number of ineligible patients randomised
30 patients were ‘randomised incorrectly’, some were not eligible and some were given the wrong treatment (exact numbers unclear, but it appeared that around 10 of the 30 were not eligible and 20 were randomised incorrectly)

Number of eligible patients not randomised (and a summary of the reasons)
None</td>
<td>Key eligibility criteria
Prehospital cardiopulmonary arrest patients (at least five feet tall). Initial airway management had to be performed by paramedics.

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>ET(n=90)</th><th>EGTA(n=85)</th></tr>
<tr><td>Age (mean)</td><td>64 (SD 17)</td><td>69 (SD 14)</td></tr>
<tr><td>Bystander CPR</td><td>12</td><td>12</td></tr>
<tr><td>Downtime (mins)</td><td>6.01 (5.90)</td><td>6.76 (SD 7.57)</td></tr>
<tr><td>Time to paramedics arrival (min)</td><td>8.15 (SD 6.73)</td><td>8.63 (SD 8.18)</td></tr>
<tr><td>Positive cardiac history %</td><td>72</td><td>66</td></tr>
</table>

Notes

The authors stated that some of the patients who were felt to be inadequately ventilated with the EGTA may have received the ET due to paramedic bias.</td>
</tr>
</table>

<table>
<tr><th>General trial details</th><th>Recruitment</th><th>Population</th></tr>
<tr>
<td>Trial reference and source review
(Rabitsch et al., 2003), (Lecky et al., 2008)

Country
Austria

Intervention and comparator
Oesophageal-Tracheal Combitube (ETC) versus conventional tracheal airways (ETA)

Sequence generation method
Day of month: Conventional ETA on even days and ETC on odd days

Reason for using quasi-random method
NR

Allocation concealment method
None

Type of consent obtained
NR</td>
<td>Target sample size
NR

Number of recruiting centres
1

Recruitment period
12 months

Number actually randomised
172

Estimated monthly rate of randomisation, per centre
14

Number of ineligible patients randomised
NR

Number of eligible patients not randomised (and a summary of the reasons)
NR</td>
<td>Key eligibility criteria
Non-traumatic cardiac arrest patients aged 18 years or more requiring immediate airway management outside hospital. Height >1.25m.

Key characteristics of population actually recruited (including all pre-specified prognostic indicators)

<table>
<tr><th>Characteristics</th><th>ETA (n=83)</th><th>ETC (n=89)</th></tr>
<tr><td>Age (SD)</td><td>54.7 (20.4)</td><td>60.7 (16.2)</td></tr>
<tr><td>Bystander CPR</td><td>8</td><td>11</td></tr>
<tr><td>Time to physicians arrival, minutes (SD)</td><td>4.3 (4.1)</td><td>4.5 (3.8)</td></tr>
</table>

Notes
If intubation failed with the initially randomised airway device after the 2nd attempt the alternate airway was used for airway management.</td>
</tr>
</table>

References

ARRICH, J., HOLZER, M., HERKNER, H. & MULLNER, M. 2009. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev*, CD004128.

BAJAJ, N., UDANI, R. H. & NANAVATI, R. N. 2005. Room air vs. 100 per cent oxygen for neonatal resuscitation: a controlled clinical trial. *J Trop Pediatr,* 51, 206-11.

BERNARD, S. A., GRAY, T. W., BUIST, M. D., JONES, B. M., SILVESTER, W., GUTTERIDGE, G. & SMITH, K. 2002. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med,* 346, 557-63.

BICKELL, W. H., WALL, M. J., JR., PEPE, P. E., MARTIN, R. R., GINGER, V. F., ALLEN, M. K. & MATTOX, K. L. 1994. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med,* 331, 1105-9.

BULGER, E. M., MAY, S., KERBY, J. D., EMERSON, S., STIELL, I. G., SCHREIBER, M. A., BRASEL, K. J., TISHERMAN, S. A., COIMBRA, R., RIZOLI, S., MINEI, J. P., HATA, J. S., SOPKO, G., EVANS, D. C., HOYT, D. B. & INVESTIGATORS, R. O. C. 2011. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Ann Surg,* 253, 431-41.

BUNN, F., ROBERTS, I., TASKER, R. & AKPA, E. 2004. Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients. *The Cochrane database of systematic reviews*, CD002045.

CALDWELL, F. T. & BOWSER, B. H. 1979. Critical evaluation of hypertonic and hypotonic solutions to resuscitate severely burned children: a prospective study. *Ann Surg,* 189, 546-52.

COOPER, D. J., MYLES, P. S., MCDERMOTT, F. T., MURRAY, L. J., LAIDLAW, J., COOPER, G., TREMAYNE, A. B., BERNARD, S. S., PONSFORD, J. & INVESTIGATORS, H. T. S. S. 2004. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *JAMA,* 291, 1350-7.

DUTTON, R. P., MACKENZIE, C. F. & SCALEA, T. M. 2002. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. *J Trauma,* 52, 1141-6.

EVANS, P. A., GARNETT, M., BOFFARD, K., KIRKMAN, E. & JACOBSON, B. F. 1996. Evaluation of the effect of colloid (Haemaccel) on the bleeding time in the trauma patient. *J R Soc Med,* 89, 101P-4P.

GAUSCHE, M., LEWIS, R. J., STRATTON, S. J., HAYNES, B. E., GUNTER, C. S., GOODRICH, S. M., POORE, P. D., MCCOLLOUGH, M. D., HENDERSON, D. P., PRATT, F. D. & SEIDEL, J. S. 2000. Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: a controlled clinical trial. *JAMA,* 283, 783-90.

GOLDENBERG, I. F., CAMPION, B. C., SIEBOLD, C. M., MCBRIDE, J. W. & LONG, L. A. 1986. Esophageal gastric tube airway vs endotracheal tube in prehospital cardiopulmonary arrest. *Chest,* 90, 90-6.

HALLIDAY, H. L. & SWEET, D. G. 2001. Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term. *Cochrane Database of Systematic Reviews,* Issue 1. Art. No., CD000500. DOI: 10.1002/14651858.CD000500.

HYPOTHERMIA AFTER CARDIAC ARREST STUDY, G. 2002. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med,* 346, 549-56.

JAMES, M. F., MICHELL, W. L., JOUBERT, I. A., NICOL, A. J., NAVSARIA, P. H. & GILLESPIE, R. S. 2011. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth,* 107**,** 693-702.

KWAN, I., BUNN, F. & ROBERTS, I. 2003. Timing and volume of fluid administration for patients with bleeding. *Cochrane Database Syst Rev***,** CD002245.

LAURENT, I., ADRIE, C., VINSONNEAU, C., CARIOU, A., CHICHE, J. D., OHANESSIAN, A., SPAULDING, C., CARLI, P., DHAINAUT, J. F. & MONCHI, M. 2005. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. *J Am Coll Cardiol,* 46**,** 432-7.

LECKY, F., BRYDEN, D., LITTLE, R., TONG, N. & MOULTON, C. 2008. Emergency intubation for acutely ill and injured patients. *Cochrane Database Syst Rev***,** CD001429.

LINDER, N., ARANDA, J., TSUR, M., MATOTH, I., YATSIV, I., MANDELBERG, H., ROTTEM, M., FEIGENBAUM, D., EZRA, Y. & TAMIR, I. 1988. Need for endotracheal intubation and suction in meconium-stained neonates. *The Journal of pediatrics,* 112**,** 613-615.

PEREL, P. & ROBERTS, I. 2011. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev***,** CD000567.

RABITSCH, W., SCHELLONGOWSKI, P., STAUDINGER, T., HOFBAUER, R., DUFEK, V., EDER, B., RAAB, H., THELL, R., SCHUSTER, E. & FRASS, M. 2003. Comparison of a conventional tracheal airway with the Combitube in an urban emergency medical services system run by physicians. *Resuscitation,* 57**,** 27-32.

RAMJI, S., AHUJA, S., THIRUPURAM, S., ROOTWELT, T., ROOTH, G. & SAUGSTAD, O. D. 1993. Resuscitation of asphyxic newborn infants with room air or 100% oxygen. *Pediatr Res,* 34**,** 809-12.

RAMJI, S., RASAILY, R., MISHRA, P. K., NARANG, A., JAYAM, S., KAPOOR, A. N., KAMBO, I., MATHUR, A., SAXENA, N. C. & SAXENA, B. N. 2003. Resuscitation of Asphyxiated Newborns with Room Air or 100%Oxygen at Birth: A Multicentric Clinical Trial. *Indian Pediatrics,* 40**,** 510-517.

SAUGSTAD, O. D., RAMJI, S., SOLL, R. F. & VENTO, M. 2008. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. *Neonatology,* 94**,** 176-82.

SAUGSTAD, O. D., ROOTWELT, T. & AALEN, O. 1998. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics,* 102**,** e1.

TOMA, A., NANEA, M., SCHEINER, M., MITU, R., PETRESCU, I. & MATU, E. 2006a. Efectele gazului folosit pentru reanimarea non-nascutului asupra hemodinamicii post-resuscitare (articles in Romanian, abstract in English); in: Asfixia Perinatala. Primul Congress National de Neonatologie cu Participare Internationala, Cluj, 2006. *Medicala Universitara 'Iuliu Hatieganau'***,** 34-44.

TOMA, A., SARBU, A., POPESCU, O., MITU, A. & DOBRESCU, M. 2006b. Room air versus oxygen in the resuscitation of term infants. *E-PAS,* 59**,** 2860.201.

TOMA, A. I., ALBU, D. F., DAMBENAU, I. M., CONSTANTINESCU, A., NANEA, M., SCHEINER, M., VAMESCU, B., LANCU, M. & GHINEA, R. 2007, abstract. 21% versus 100% oxygen in the resuscitation of term infants. Prague. *ESPR*.

TURNER, J., NICHOLL, J., WEBBER, L., COX, H., DIXON, S. & YATES, D. 2000. A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. *Health Technol Assess,* 4**,** 1-57.

VASSAR, M. J., FISCHER, R. P., O'BRIEN, P. E., BACHULIS, B. L., CHAMBERS, J. A., HOYT, D. B. & HOLCROFT, J. W. 1993. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. The Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. *Arch Surg,* 128**,** 1003-11; discussion 1011-3.

VENTO, M., ASENSI, M., SASTRE, J., GARCIA-SALA, F. & VINA, J. 2001. Six years of experience with the use of room air for the resuscitation of asphyxiated newly born term infants. *Biol Neonate,* 79**,** 261-7.

VENTO, M., ASENSI, M., SASTRE, J., LLORET, A., GARCIA-SALA, F. & VINA, J. 2003. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. *J Pediatr,* 142**,** 240-6.

VENTO, M., SASTRE, J., ASENSI, M. A. & VINA, J. 2005. Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. *Am J Respir Crit Care Med,* 172**,** 1393-8.

WISWELL, T. E., GANNON, C. M., JACOB, J., GOLDSMITH, L., SZYLD, E., WEISS, K., SCHUTZMAN, D., CLEARY, G. M., FILIPOV, P., KURLAT, I., CABALLERO, C. L., ABASSI, S., SPRAGUE, D., OLTORF, C. & PADULA, M. 2000. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. *Pediatrics,* 105**,** 1-7.

Important prognostic indicators and magnitudes of group difference

Review	Important prognostic indicator	Magnitude of group baseline difference deemed to be important	Source
Room air or pure oxygen for newborns Endotracheal intubation for newborns	Gestational age	<28 weeks vs >28 weeks ≥1 week difference, up to 32 weeks 32-33 weeks vs 34-36 weeks 34-36 weeks vs 37-41 weeks 37 weeks vs 40 weeks	Clinical advice Manktelow et al[1] Kramer et al [2] Tomashek et al[3] Altman et al[4]
Colloids versus crystalloids for fluid resuscitation Timing and volume of fluid administration Hypertonic versus near isotonic crystalloids for fluid resuscitation in critically ill patients	TRISS or	≥5% difference	Gabbe et al[5], difference decided arbitrarily
	ISS or	Differences in score categories*	Stevenson et al[6]
	Age	≥5 year difference	Gabbe et al[5]†
Hypothermia for neuroprotection after cardiopulmonary resuscitation	Age or	≥2 year difference	Bernard 2002[7]
	Time from collapse to return of spontaneous circulation	≥1.5 minute difference	Bernard 2002[7]
Intubation for acutely ill and injured patients	Age or	≥2 year difference for adults, ≥1 year for children	Bernard 2002)[7] - similar populations (cardiac arrest) as the hypothermia review
	Time to arrive on scene or	≥1 minute difference	Decided arbitrarily
	Proportion of patients receiving bystander cardiopulmonary resuscitation	≥5% difference	Decided arbitrarily

ISS - Injury Severity Score, TRISS - Trauma and Injury Severity Score. *Injuries categorised as being minor, moderate, serious, severe, or critical. †This study questions the value of the age cut-off (≤55 years or >55 years) used in TRISS, so we also considered age separately. The 5 year difference was decided arbitrarily and was larger than the 2 year differences used for the hypothermia and intubation trials because much younger populations (without cardiac arrest) were studied.

References

1. Manktelow, B.N., et al., *Population-based estimates of in-unit survival for very preterm infants.* Pediatrics, 2013. **131**(2): p. e425-32.
2. Kramer, M.S., et al., *The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System.* JAMA : the journal of the American Medical Association, 2000. **284**(7): p. 843-9.
3. Tomashek, K.M., et al., *Differences in mortality between late-preterm and term singleton infants in the United States, 1995-2002.* The Journal of pediatrics, 2007. **151**(5): p. 450-6, 456.e1.
4. Altman, M., et al., *Neonatal morbidity in moderately preterm infants: a Swedish national population-based study.* The Journal of pediatrics, 2011. **158**(2): p. 239-44.e1.

5. Gabbe, B.J., P.A. Cameron, and R. Wolfe, *TRISS: does it get better than this?* Acad Emerg Med, 2004. **11**(2): p. 181-6.
6. Stevenson, M., et al., *An overview of the injury severity score and the new injury severity score.* Inj Prev, 2001. **7**(1): p. 10-3.
7. Bernard, S.A., et al., *Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.* N Engl J Med, 2002. **346**(8): p. 557-63.

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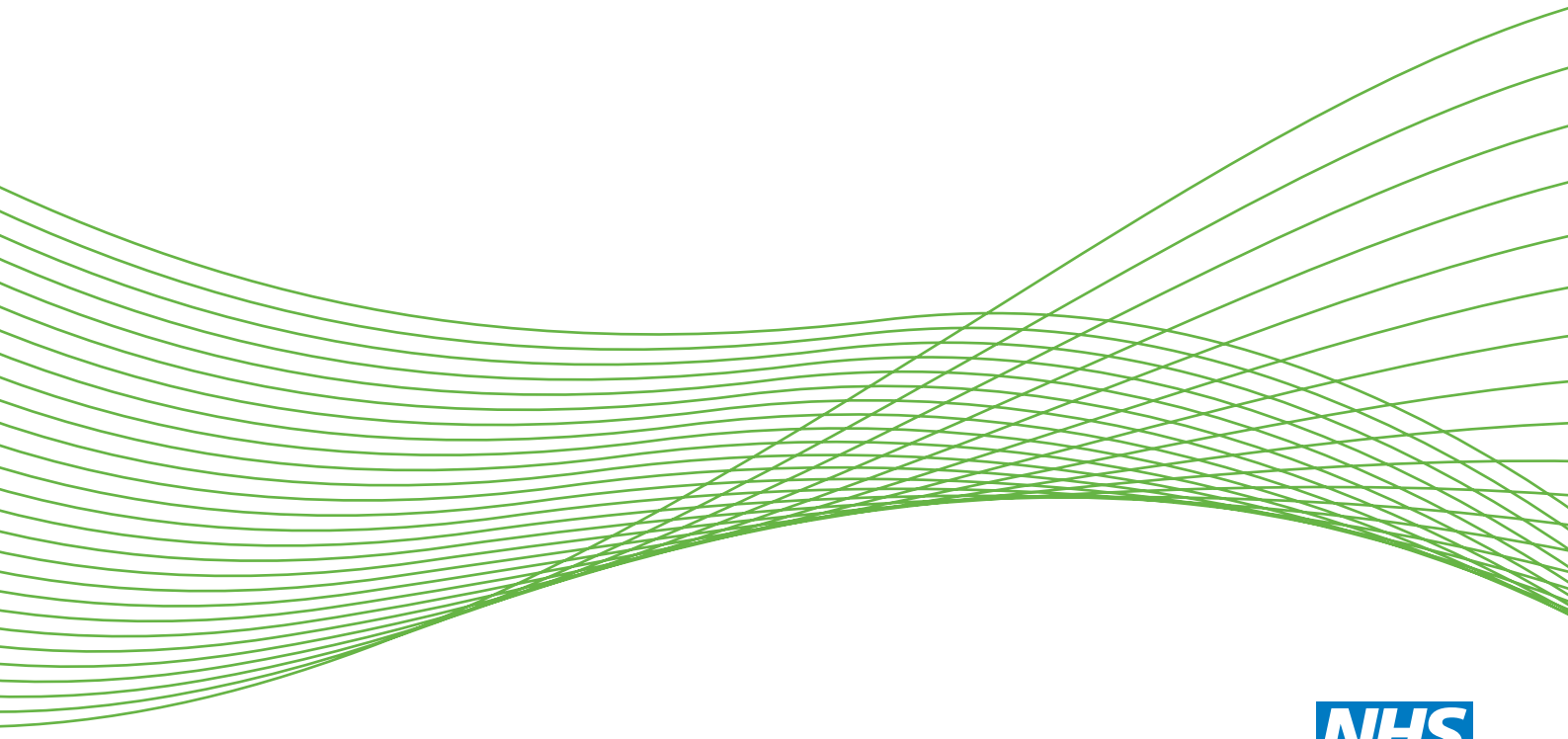
The delivery of chemotherapy at home: an evidence synthesis

Mark Corbett, Morag Heirs, Micah Rose, Alison Smith, Lisa Stirk, Gerry Richardson, Daniel Stark, Daniel Swinson, Dawn Craig and Alison Eastwood



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Abstract

The delivery of chemotherapy at home: an evidence synthesis

Mark Corbett,[1] Morag Heirs,[1] Micah Rose,[1] Alison Smith,[1] Lisa Stirk,[1] Gerry Richardson,[2] Daniel Stark,[3] Daniel Swinson,[4] Dawn Craig[1] and Alison Eastwood[1]*

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Background: Recent policy and guidance has focused on chemotherapy services being offered closer to home, but the clinical and economic implications of this are uncertain.

Objectives: To compare the impact of delivering intravenous chemotherapy in different settings on a range of outcomes, including quality of life, safety and costs.

Design: Multimethods approach: systematic review of clinical effectiveness, qualitative and cost-effectiveness studies; description of the patient pathway and brief survey of current provision; and development of a decision model to explore aspects of cost-effectiveness.

Setting: Provision of intravenous chemotherapy.

Participants: Chemotherapy patients.

Interventions: Setting in which chemotherapy was administered (home, community or outpatient).

Outcome measures: Safety, quality of life, preference, satisfaction, opinions/experiences, social functioning, clinical outcomes, costs and resource/organisational issues.

Data sources: Sixteen electronic databases (including MEDLINE, EMBASE and The Cochrane Library) were searched from inception to October 2013 for published and unpublished studies.

Review methods: Two reviewers independently screened potentially relevant studies, extracted data and quality assessed the included studies. Study validity was evaluated using appropriate quality assessment tools. Clinical effectiveness and cost-effectiveness studies were summarised narratively, and qualitative studies were synthesised using meta-ethnography.

Results: Of the 67 eligible studies, 25 were comparative, with nine including a concurrent economic evaluation. Although some of the 10 randomised trials were designed to minimise avoidable biases, slow recruitment rates and non-participation of eligible patients for setting-related reasons meant that trial sample sizes were small and populations were inherently biased to favour the home or community settings. There was little evidence to suggest differences between settings in terms of quality of life, clinical outcomes, psychological outcomes or adverse events. All nine economic evaluations were judged as having low or uncertain quality, providing limited evidence to draw overall conclusions. Most were cost–consequence analyses, presenting cost outcomes alongside trial results but deriving no summary

measure of benefit. Poor resource use reporting and use of different perspectives across settings made results difficult to compare. Seventeen qualitative studies (450 participants) were judged as moderate to good quality, although all compared new or proposed services with existing outpatient facilities and biased samples were used. The three main lines of argument were barriers to service provision, satisfaction with chemotherapy and making compromises to maintain normality. Most patients made explicit trade-offs between the time and energy required for outpatient chemotherapy, which reduced quality of life, and an increased sense of safety. A patient pathway was described, informed by expert advice and a brief survey of NHS and private providers, which identified wide variation in the ways in which home and community chemotherapy was delivered. Considering limitations of the available data and variation in provision, cost-effectiveness modelling results were not robust and were viewed as exploratory only; the results were highly unstable.

Conclusions: Primary studies comparing settings for administering intravenous chemotherapy appear difficult to conduct. Consequently, few robust conclusions can be made about the clinical effectiveness and cost-effectiveness. Qualitative studies indicate that the patient time and energy required for outpatient chemotherapy reduces quality of life. A nested randomised controlled trial within a larger observational cohort of patients is proposed to enhance recruitment and improve generalisability of results. Future economic evaluations require detailed patient characteristic, resource use, cost and quality-of-life data, although their results are likely to have limited generalisability.

Study registration: This study is registered as PROSPERO CRD42013004851.

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List of abbreviations

A&E	accident and emergency
CRD	Centre for Reviews and Dissemination
CUA	cost–utility analysis
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30 items)
EPPI	Evidence for Policy and Practice Information
EQ-5D	European Quality of Life-5 Dimensions
FLIC	Functional Living Index Cancer
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HaH	Healthcare at Home
ICER	incremental cost-effectiveness ratio Profile
NICE	National Institute for Health and Care Excellence
PedsQL	Paediatric Quality of Life Scale
Ph.D.	Doctor of Philosophy
POQOLS	Paediatric Oncology Quality of Life Survey
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SD	standard deviation
VAT	value-added tax

Plain English summary

There is an increasing focus in the NHS on delivering care closer to home. Chemotherapy treatment is offered in community, home and hospital settings. To explore the differences between these settings for patients and service providers, a review of the existing evidence and a survey of current service provision were undertaken. An economic model was developed also.

The systematic literature review identified little robust evidence. The studies had small sample sizes and populations likely to prefer home or community settings. They demonstrated little difference in terms of quality of life, physical or emotional symptoms, or adverse events. Previous economic evaluations provided limited evidence on cost-effectiveness and for informing the economic model.

The studies about patient experiences indicated that decisions about treatment setting are strongly influenced by a desire for normality. The time and energy required for outpatient chemotherapy reduces overall quality of life and so patients prefer alternative settings. However, competing factors and patient preference reflected individual situations.

The survey showed wide variation in the current provision of home and community chemotherapy in the NHS. Eligibility varied by provider, with chemotherapy regimen and patient response to initial treatment in hospital important determinants.

The economic modelling was limited by a lack of data and by the broad variation in NHS treatment delivery pathways.

A better design for future research might be to nest a randomised trial within a larger observational study. For a reliable economic evaluation, broad observational data will be needed to explore variations and ensure generalisability.

Scientific summary

Background

Throughout the NHS there is an increasing focus on developing service models of care which meet the needs of patients, with care being delivered locally wherever possible to maximise convenience and centralised where necessary to improve outcomes. For cancer treatment, recent policy and guidance has focused on chemotherapy services being offered not only in cancer centres and cancer units but also in community and home settings, while maintaining safety and quality and delivering an efficient service.

Many hospitals across England and Wales are delivering chemotherapy services at full capacity, with increasing demand for services putting a strain on NHS capacity resources. This can have a detrimental effect on patient experience as a result of longer waiting times. Delivering chemotherapy closer to home may be an approach by which the NHS could relieve demand for outpatient services while maintaining or even improving patient care. Nevertheless, the clinical and economic implications of delivering chemotherapy closer to home are uncertain.

Objectives

This aim of this study was to compare the impact of delivering intravenous chemotherapy in different settings (home, community and hospital outpatient) on a range of outcomes, including quality of life, safety and costs.

Methods

A systematic review of clinical effectiveness, qualitative and cost-effectiveness studies was undertaken. A decision model was developed to explore aspects of cost-effectiveness. Data from published and unpublished studies were sought systematically from 16 electronic databases (including MEDLINE, EMBASE and The Cochrane Library, searched from inception) in March 2013; updated searches of the most relevant databases were undertaken in October 2013. Reference lists and Google (www.google.co.uk) searches were used to identify any further studies.

Studies of cancer patients receiving intravenous chemotherapy in two or more of the following settings were eligible: home, community based (e.g. general practitioner practice, mobile bus, or community hospital) and hospital outpatient. Within-setting comparisons were also eligible. Studies had to report at least one of the following outcomes: safety, quality of life, preference, satisfaction, social functioning, clinical outcomes (such as self-rated health), costs or resource/organisational issues. Any type of comparative design (including economic evaluation) was eligible. Single-setting studies were also identified and included, but were used in the review only where they might usefully supplement the comparative study evidence (this happened only for qualitative studies). Quality assessment tools, specific to particular study designs, were used to evaluate the validity of the included studies.

Two reviewers independently screened all of the potentially relevant studies, and data extracted and quality assessed those included. Discrepancies were resolved by discussion. Clinical effectiveness and cost-effectiveness studies were summarised narratively; qualitative studies were synthesised using meta-ethnography.

To supplement the published evidence and to gain insight into the variation in current NHS practice, a survey was undertaken, canvassing views from relevant professionals about their experience of providing home and community chemotherapy. The results of the survey were intended to help to describe the patient pathway and inform the development of a decision model. A lack of evidence led to a simple model based on one UK trial (OUTREACH) being developed. The aim of the model was to assess the cost-effectiveness of intravenous chemotherapy delivered in the home, community or outpatient setting in a population considered eligible for home treatment. The model was conducted from a NHS perspective using a 12-week time horizon. The summary measure of benefit was quality-adjusted life-years.

Results

The literature searches identified 4272 references and 245 potentially relevant full papers were screened. A total of 67 studies were included: 25 comparative studies and 42 single-setting studies. Of the 25 comparative studies, 10 were randomised controlled trials (RCTs) and 15 were non-randomised studies; nine of the comparative studies included a concurrent full economic evaluation. Most studies evaluated adult populations and compared home and hospital outpatient settings.

The 10 randomised trials recruited 482 participants in total. Several trials were appropriately designed to minimise avoidable biases. However, slow recruitment rates and the non-participation of eligible patients for setting-related reasons meant that trial sample sizes were small and populations were inherently biased to favour the home or community settings. This bias was evident in the results for the preference and satisfaction outcomes, although these data were limited as only one trial studied strength of preference. Perhaps surprisingly, there was little evidence to suggest differences between settings in terms of quality of life, clinical outcomes or psychological outcomes. Adverse event data also did not suggest any important differences between settings; these data were limited by the small study sizes. The 15 non-randomised studies added little to the randomised trial evidence: the main limitations were the small populations and a high risk that the study results were biased as a result of confounding.

All nine of the economic evaluations were judged as being of low or uncertain quality. Most were cost–consequence analyses, which presented cost outcomes alongside clinical trial results but derived no summary measure of benefit. Only one evaluation assessed patient health-related quality of life and reported utility outputs (many studies used patient preference as an outcome measure). Poor reporting of resource use and use of different perspectives across different settings made the results difficult to compare. High levels of uncertainty made it difficult to ascertain whether or not costs or outcomes differed between settings. In general, these studies provided limited evidence from which to draw an overall conclusion regarding cost-effectiveness or to inform or populate a decision model.

The 17 qualitative studies evaluated the opinions and experiences of more than 450 participants in total, including patients, family members and health-care professionals. Generally, study quality was moderate to good but most studies did not appear to consider the impact of the researcher on data collection and analysis. Overall, data were grouped under three main lines of argument: barriers to service provision, satisfaction with chemotherapy and making compromises to maintain normality. The last of these was seen as key to being able to survive a difficult time and look forward.

Most patients made explicit trade-offs to maximise their resources (such as time, money and energy). Normality was maintained more easily when family life was minimally interrupted, the impact of cancer on daily life and family members was controllable, and patients were able to participate in activities of value. Time spent travelling and waiting for treatment meant less time and energy for normal life. Outpatient settings were most often associated with increased confidence in staff ability to deal with adverse reactions, but there was evidence that good, visible communication between an expert centre and a community or home location could alleviate some safety concerns. Based on available data, the time and energy consumed by outpatient treatment reduced overall quality of life such that patients preferred

alternative treatment settings. These themes were particularly evident in accounts from patients receiving palliative treatment and from parents of children with cancer.

We circulated the survey widely and it was passed on further by initial contacts. This made it impossible to calculate a response rate. Twenty-two NHS organisations (all in England) and nine private providers responded to the survey. The results suggested wide variation in the ways in which home and community chemotherapy was delivered. It was evident that more patients were eligible for community treatment than home treatment and that chemotherapy regimen and patient performance were important determinants of eligibility. Private providers were frequently used to deliver treatment in the home setting and appeared to use more selective eligibility criteria (e.g. treating patients only after two or more cycles had been delivered in hospital). Several NHS organisations highlighted that value-added tax savings associated with home chemotherapy were a significant motivator for providing such a service.

We anticipated that we would be able to develop and populate a robust decision model through combination of the published evidence and the survey. However, limitations of the available data meant that results from the cost-effectiveness model were highly unstable and should be viewed as exploratory rather than robust.

In the base-case analysis, intravenous chemotherapy in the community setting was the most cost-effective option, but none of the settings had a high probability of being the most cost-effective. Sensitivity analyses highlighted the fragility of the results to parameter changes. Adjusting cost values within plausible ranges also altered the preferred treatment setting. There was significant uncertainty over which treatment settings were cost-effective. Robust data to inform cost-effectiveness modelling would be needed to resolve this uncertainty, as well as further consideration of service configuration and appropriate patient pathways.

Conclusions

The results of this study highlighted not only avoidable study design and reporting limitations but also inherent and sometimes unavoidable difficulties that arise during primary studies of chemotherapy settings. Several studies were designed appropriately to minimise avoidable biases but implementing randomised trials in this area appears difficult in terms of patient accrual and recruiting unbiased populations. These issues impacted on the concurrent economic evaluations and were further compounded by poor reporting of cost and resource data. Consequently, few robust conclusions can be made about the clinical effectiveness and cost-effectiveness of different settings. High uncertainty remains owing to trial sizes that were potentially too small to detect effects reliably. It was unclear whether or not the quality-of-life instruments used in the studies were sensitive enough to detect differences in quality of life between chemotherapy settings. Accordingly, the results of the exploratory cost-effectiveness model based on the OUTREACH trial were not robust and the cost-effectiveness results of the model should be interpreted with caution.

Qualitative studies were more informative. They indicated that decisions and preferences about intravenous chemotherapy treatment setting are strongly influenced by a desire to maintain normality. Patient time and energy required for outpatient chemotherapy reduces overall quality of life enough for patients to prefer alternative treatment settings. However, compromises were needed to balance competing factors and patient preference for specific locations reflecting individual situations. Limitations of the qualitative studies were that all evaluated a new or proposed service against an existing (perhaps struggling) hospital outpatient setting, and participants were drawn from biased samples.

Implications for research

Considering the likely challenges involved in performing further RCTs using conventional study designs, a better design might be to nest a RCT within a larger observational cohort of patients: ambivalent patients could be randomised and patients with preferences could receive their preferred setting. Such a study might also incorporate (into questionnaires) the qualitative data themes identified in this review. Efficacy estimates would result from the randomised component of the study. Any additional influence of motivational factors could be studied by comparing randomised and non-randomised patients treated in the same setting. The results from this nested design should also indicate whether or not there are any clinical or demographic differences between the different populations at baseline, and produce estimates of likely rates of uptake of the different settings, to help inform future service provision. Such a study should more clearly identify and quantify issues such as setting-related adverse events, waiting times, anxiety and transport problems, and indicate how their prevalence and impact might vary according to patient characteristics.

For an economic evaluation to be reliable, detailed patient characteristics, resource use, cost and quality-of-life data are needed. The ideal collection method for these parameters is a large multicentre RCT that incorporates a wide variety of providers. However, a key theme that emerged from the review and survey concerned a high level of variation in current practice in the NHS. This variation makes it unlikely that a RCT will provide sufficient evidence for a broad economic evaluation. We surmise that, in order to explore this variation and mitigate generalisability issues, broad observational data will be necessary. Information from large observational data sets such as the Systemic Anti-Cancer Therapy and the General Practice Research Database could be linked to provide a clearer portrait of current provision.

Study registration

This study is registered as PROSPERO CRD42013004851.

Funding

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Chapter 1 Background

Historically, chemotherapy treatment for cancer patients was delivered in hospital. More than 10 years ago, a *BMJ* editorial noted a shift in chemotherapy practice in the UK from inpatient to outpatient ambulatory therapy.[1] The editorial highlighted a small but growing body of evidence suggesting that chemotherapy in the home was both safe and acceptable, but also identified a need for further exploration of patient selection and cost-effectiveness.

Potential benefits of receiving chemotherapy treatment at home include less travelling to hospital facilities, reduced risk of hospital-acquired infection, receiving treatment in the comfort and security of the home, less disruption to family life and an increased feeling of control over treatment and illness.[2] Potential concerns for patients include increased feelings of isolation, decreased contact with hospital staff (such as specialist nurses) and other patients, feelings of insecurity from a perception of reduced support outside the hospital setting, and the possibility of less continuity of care.[3]

Safety is often perceived as being a key issue in the delivery of chemotherapy owing to the toxicity of the drugs, the costs of management of preventable toxicities and the need for specialist skills to administer and monitor treatment. The OUTREACH trial report indicated that clinicians were reluctant to refer patients for home or general practice chemotherapy in part because of patient safety concerns.[4]

It is important to ensure that the risks of toxicity are managed by a cohesive multiprofessional team, that problems with toxicity are identified promptly and correctly managed and that concordance with treatment is optimised if outcomes are to be maintained. Severe side effects can be very disturbing and may influence a patient's decision to continue with treatment; this is true in any setting, but may possibly have a longer term impact on patients when experienced at home. Whatever the treatment setting, severe adverse events mostly occur between treatment-days and so even outpatients experience them outside hospital. Appropriate pre-treatment assessment and patient education are key issues that apply to patients in any setting. Health-care professionals involved with the administration and monitoring of treatment need to have the relevant skills and expertise.

Throughout the NHS there has been an increasing focus on making care more centred on the needs and preferences of patients.[5] In the area of cancer services, the Cancer Reform Strategy has pledged that care will be delivered in the most clinically appropriate and convenient setting for patients.[6] The Department of Health Cancer Policy Team has produced guidance to develop chemotherapy services in the community [such as in general practitioner (GP) surgeries or patients' homes],[3] which builds on best practice guidance provided in the National Chemotherapy Advisory Group report published in 2009.[7] These documents promote the consideration of opportunities to devolve chemotherapy from cancer centres and cancer units to community settings while maintaining safety and quality, and delivering an efficient service. However, a report on how effectively strategies laid out in the Cancer Reform Strategy have been utilised to improve cancer services for patients found a lack of activity in the commissioning of services, with only 26% of primary care trusts having undertaken a cost–benefit analysis looking at different ways of delivering cancer services.[8]

These initiatives should be considered within the context of plans in England to reduce the number of centres commissioned for specialised services and focus provision in a smaller number of centres.[9] It is currently unclear if chemotherapy will be included within the definition of a specialised service, or if this will depend on the nature of the cancer being treated. Such a policy change may have implications for where cancer chemotherapy is prescribed and administered, including options for delivery closer to home.

It is likely that many outpatient facilities across England and Wales are delivering chemotherapy services at full capacity (assuming a 15% year-on-year growth in demand), and increasing strain to the service is anticipated.[7] Future demand for services is likely to increase further; increasingly early detection of cancer,

improving cancer survival and an ageing population are key factors. For hospitals without the resources to appropriately expand their capacity in terms of either staffing levels or physical space, it is likely that future patients will face longer waiting lists or a reduced service. Delivering chemotherapy closer to the home may enable hospitals to relieve the demand for hospital ward services while maintaining patients' care.

The various chemotherapy delivery practices used in the UK reflect the different challenges of, for example, large cancer centres and district general hospitals.[10] Nurse-led chemotherapy is well established within the outpatient setting but home and community delivery of chemotherapy is not currently widespread. Different geographic challenges exist for provision in remote and rural communities compared with urban centres. The Department of Health lists exemplars of NHS community chemotherapy services in Sunderland, Dorset, West Anglia, East Anglia and East Kent, and there are health-care companies who undertake chemotherapy in the community, offering services to both private and NHS providers, for example Healthcare at Home (HaH), BUPA Home Healthcare, Baxter, Calea and Alcura.[3]

Successful services are likely to be closely tailored to the local requirements and available resources, and as such are expected to vary considerably. For example, Leeds Teaching Hospitals NHS Trust does not provide intravenous chemotherapy at home, at least in part because of the logistics of covering a large and diverse catchment area; patients can receive intravenous chemotherapy in the community (at Otley community hospital) and would attend pre-treatment assessment clinics at St James's University Hospital in Leeds. Conversely, the Sunderland model covers a relatively small urban area, which allows for a range of services to be provided (*Box 1*).

BOX 1 Case study of a successful service

Case study of a successful service: Sunderland

In the Sunderland model, intravenous chemotherapy is available across three different settings according to patient choice where eligibility criteria are met (drug is given in short infusions lasting < 5 hours, or as bolus treatment that is not associated with a high risk of anaphylaxis). This model of care has been in operation since 2009 and is entirely provided by the local NHS hospital, covering a 15-mile radius from the main hospital. Initial assessments are carried out by the chemotherapy nurse prior to treatment being scheduled.

From initiation of treatment, patients choose their preferred setting. Bookings are made through a single appointment system, which allows flexibility so that patients can move between locations to suit their schedules.

- Hospital outpatient (one venue, provided 6 days per week with a Saturday clinic 8.30 a.m. to 2.30 p.m., extended working until 7.00 p.m. midweek, approximately 40 patients per day).
- Outreach service (one venue, primary care centre provided 3 days per week, approximately 15 patients per day).
- Patient home (try to group geographically, provided 4 days per week, six to eight patients per day).

Chapter 2 Introduction

Aims

This aim of the project was to investigate the impact of the delivery of intravenous chemotherapy in different settings on quality of life, safety, patient satisfaction and costs. Our focus was the provision of intravenous chemotherapy led and managed from the oncology department and delivered in the patient's home, in the community or in the hospital outpatient department.

Objectives

The project comprised four elements:

- a systematic review of the clinical and economic literature to bring together and assess the existing evidence
- a brief survey to gather information about the structure of services and variation in practice across the NHS
- a description of the general pathway for patients who will be offered chemotherapy
- the development of a decision model to compare delivery of chemotherapy for an eligible population in three settings.

In addition to the project team, an advisory group of specialist nurses, pharmacists, and patient representation was formed to help to guide each of the elements from the proposal stage through to the final report. This report details the methods and results for each element, draws together and discusses the findings and identifies the implications for health care and future research.

Chapter 3 Systematic review

Introduction

To provide a complete overview of the current published evidence base for the delivery of intravenous chemotherapy closer to home, a series of three interlinked systematic reviews was undertaken. Each review assessed a different type of evidence: comparative clinical effectiveness, cost-effectiveness and qualitative studies. We used the same methodology across reviews except where different types of evidence precluded this; any alternative methods are clearly described and signposted.

Together, the three reviews summarise the totality of the evidence base by addressing particular questions and focusing on the most appropriate type of evidence. The reviews were conducted in parallel within an explicit and pragmatic mixed-methods framework based on principles of complementarity. This approach is based loosely on the approach pioneered by the Evidence for Policy and Practice Information (EPPI) and Co-ordinating Centre (the EPPI approach).[11]

The same researchers worked on each of the three reviews to ensure a collaborative approach. Regular team meetings and discussions during study selection, data extraction and analysis promoted cross-fertilisation of ideas. Matrices were used to collate the summary findings from each of the three reviews. Commonalities and divergences between the results were identified and integrated with the findings informing the decision model. *Chapter 6* presents the meta-synthesis of all elements from the project.

Methods

Searches

The aim of the literature searches was to systematically identify research on the impact of setting (closer to home) on the delivery and outcomes of intravenous chemotherapy.

The base search strategy was constructed using MEDLINE and then adapted to the other resources searched (*Box 2*).

BOX 2 MEDLINE search strategy

MEDLINE search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

URL: http://ovidsp.ovid.com/

Date range: 1946 to week 2 March 2013.

Date of search: 25 March 2013.

1564 records identified.

BOX 2 MEDLINE search strategy (*continued*)

Search strategy

1. exp neoplasms/ (2,406,640)
2. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (2,073,583)
3. oncologic nursing/ (6088)
4. or/1-3 (2,889,785)
5. drug therapy/ (33,151)
6. Antineoplastic Combined Chemotherapy Protocols/ (97,247)
7. chemotherapy, adjuvant/ or consolidation chemotherapy/ or maintenance chemotherapy/ (27,648)
8. administration, intravenous/ or infusions, intravenous/ (46,068)
9. chemotherapy.ti,ab. (223,465)
10. systemic therapy.ti,ab. (5856)
11. intravenous drug therapy.ti,ab. (39)
12. adjuvant therapy.ti,ab. (14,653)
13. or/5-12 (357,679)
14. home care services/ or home care services, hospital-based/ (28,037)
15. *Outpatients/ (2136)
16. *Ambulatory Care/ (14,592)
17. *ambulatory care facilities/ or *outpatient clinics, hospital/ (13,416)
18. community health services/ or community health nursing/ or community health centers/ (47,800)
19. general practitioners/ or physicians, family/ or physicians, primary care/ (16,406)
20. general practice/ or family practice/ (61,185)
21. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (42,475)
22. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (15,680)
23. or/14-22 (207,550)
24. 4 and 13 and 23 (1144)
25. home infusion therapy/ (579)
26. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (719)
27. (chemotherapy adj6 service$).ti,ab. (184)
28. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (19)
29. (self-infusion adj6 home).ti,ab. (21)
30. home infusion.ti,ab. (254)
31. or/25-30 (1591)
32. 4 and 31 (751)
33. 24 or 32 (1595)
34. exp animals/ not humans/ (3,782,734)
35. 33 not 34 (1564)

The search included the following components:

1. cancer terms AND
2. chemotherapy terms AND
3. generic home care/ambulatory care terms.

These terms were combined with (OR), the following terms:

1. cancer terms AND
2. home chemotherapy terms.

No date, language or other limits were applied and, where possible, animal-only studies were excluded.

The strategy was constructed by an information specialist within the Centre for Reviews and Dissemination (CRD) and subsequently peer reviewed by another information specialist prior to use.

Search terms were identified by scanning key papers known at the beginning of the project, through discussion with the review team and the use of database thesauri.

The full strategies from all of the databases are given in *Appendix 1*.

Sources of both published and unpublished information were identified by an information specialist with input from the project team. MEDLINE and MEDLINE In Process & Other Non-Indexed Citations; Allied and Complementary Medicine Database; British Nursing Index; Cumulative Index to Nursing and Allied Health Literature; The Cochrane Library; Conference Proceedings Citation Index – Science; Dissertation Abstracts; EconLit; EMBASE; Google; Health Management Information Consortium; Inside; Office for Health Economics Health Economic Evaluations Database; PsycINFO; PubMed; Social Policy and Practice; ClinicalTrials.gov and Current Controlled Trials databases and the Google search engine were searched.

Databases were searched from date of inception to March 2013. Update searches were undertaken in October 2013.

Reference searches of all included randomised controlled trials (RCTs) and relevant systematic reviews were undertaken. Where necessary, authors of eligible studies were contacted for further information and experts in the field were contacted to see whether or not they had access to further material.
We contacted private providers of home care through the National Clinical Homecare Association (including HaH, Bupa, Baxter, Calea and Alcura) to identify unpublished reports, evaluations or resource information.

We also contacted the Medicines and Healthcare products Regulatory Agency to request information on suspected adverse drug reactions and adverse events for intravenous home chemotherapy drugs. Route of administration was available, but the system does not store information on the setting where the drug was given or the adverse event occurred. Therefore, no data relevant to this project could be collated.

Inclusion criteria

Population
Cancer patients receiving intravenous chemotherapy.

Interventions and comparators
Studies comparing intravenous chemotherapy in two (or more) of the following settings:

- home setting (includes nursing homes)
- community-based setting (e.g. GP practice, community clinic, community hospital or mobile units)
- hospital outpatient setting.

Within-setting comparisons were eligible if the study compared different organisational or management approaches.

Outcomes
Any of the following:

- safety
- patient quality of life
- preference
- satisfaction (including treatment compliance/adherence)
- social functioning
- clinical outcomes
- patient and carer opinions and experiences
- costs
- resource/organisational issues (including access).

The clinical outcomes of interest were self-rated health or measures of performance status.

Study designs
Any type of comparative design was eligible. To obtain information about patient quality of life, satisfaction, preferences and opinions, studies that reported results for only one eligible setting and qualitative research (any of the three settings) were considered, providing that they had a stated aim to evaluate one or more of these outcomes. Given the review focus on home and community settings, and the potential diversity and likely volume of these studies in an outpatient setting, we focused on studies of the home and community settings.

Full economic evaluations that compared two or more eligible settings and considered both costs and consequences (including cost-effectiveness, cost–utility or cost–benefit analyses) were eligible.

Screening and study selection
Two researchers independently screened all titles and abstracts obtained using the predefined eligibility criteria. Discrepancies were resolved by consensus, with recourse to a third researcher where necessary. Full manuscripts of potentially relevant studies were obtained where possible and were screened in duplicate. Studies in any language were eligible for inclusion.

Data extraction and quality assessment
Studies were assessed for quality as part of the data extraction process using criteria relevant to the topic and study designs included. Data were extracted into structured forms using a pre-piloted form in EPPI-Reviewer (EPPI-Centre, Institute of Education, University of London, London, UK). Piloting was undertaken by each researcher involved with the process and refined as necessary prior to full data extraction to ensure consistency. Data extraction and quality assessment was conducted by one researcher and checked by a second researcher for accuracy, with any discrepancies resolved by discussion or by recourse to a third researcher where necessary.

Clinical studies
Data were extracted on details of study methods, country and geographical region in which the study was conducted, whether it was single or multicentre, dates over which the study was conducted, patient characteristics, interventions, comparators where appropriate, all relevant outcome measures and results.

The quality of included comparative studies was assessed using criteria appropriate to the study design, adapted from published checklists.[12]

Randomised controlled trials
Randomised controlled trials were assessed using the Cochrane risk of bias tool, which focuses on the domains shown to impact on the trial results in particular (selection, performance and detection biases and attrition).[13] The tool was modified to incorporate assessment of baseline imbalances when we evaluated selection bias.[14]

Non-randomised comparative studies

Study quality evaluations were based on recently published papers detailing methodological issues and assessment of bias in non-randomised studies.[15–18] Confounding variables (variables other than the intervention being studied, which might affect study outcomes when groups are compared) are known to be a very important source of bias in non-randomised studies.[19] As there were many potentially important confounders for our review question, we focused our assessment on evaluation of the risk of bias due to confounding. This was done by answering the following questions:

1. How were the groups formed?
2. Were the effects of any confounders taken into consideration during the design and/or statistical analysis stages?
3. What methods were used to control for confounders?
4. Were data on the measured confounders recorded precisely enough?
5. Were any key confounders not controlled for?

The important confounders we considered were type of cancer, stage of cancer, type of chemotherapy, age, performance status [e.g. Karnofsky, Eastern Cooperative Oncology Group (ECOG) or Lansky scores], quality of life, treatment intent (curative or palliative) and distance from hospital. These confounders were chosen for their potential to affect outcomes such as quality of life and patient satisfaction. Some of these confounders are correlated.

Where these confounders were not measured, and not taken into account in the design or analysis of the study, the study results were deemed likely to be at a high risk of bias. Studies where such details were not clear were judged to have an unclear risk of bias. Given the non-randomised nature of the studies and the lack of assurance provided about the methods used, the implications of an unclear risk of bias judgement are similar to those of a high risk of bias judgement and the study results should not be interpreted as being reliable.

Where the answer to question 2 was 'yes', the details of which confounders were controlled for were recorded and the remaining questions were answered; the overall risk of bias judgement (from confounding) was then made based on the answers to questions 3, 4 and 5. Where the answer to question 2 was 'no' or 'not reported', a high or unclear risk of bias judgement was made and the remaining questions were not answered. An assessment of whether or not there was evidence that potential confounders did not actually result in confounding was also made when considering question 2.

For non-randomised studies there is evidence that confounding may not, on average, cause bias in the estimation of adverse effects.[17] We considered this during our assessments according to how likely a given adverse effect (as defined in individual studies) might be affected by confounding.

As cost and resource outcomes were extracted to inform the review's economic modelling, formal synthesis and quality assessments were not routinely performed for these outcomes.

Non-comparative studies were not extracted or quality assessed, but they are listed for reference in *Appendix 2*.

Cost-effectiveness studies

Data extracted from economic evaluations included interventions compared study population; dates to which the data related; measures of effect; direct costs (medical and non-medical); currency used; utilities/measure of health benefit; and results and details of any decision modelling applied. The quality assessment of the economic evaluations was informed by use of the Drummond 36-point checklist.[20] The purpose of the review was to provide an overview of the current cost-effectiveness evidence base and help to inform the development of a de novo decision model. Any additional information that could aid development of a de novo decision model was also extracted.

Qualitative studies

Qualitative studies were assessed for methodological quality using criteria based on the work of Mays and Pope, among others.[21–23] As with the quantitative studies, the focus was on those domains which are expected to influence the reliability of the findings. Domains included transparency and documentation of the data collection and analysis processes, description and justification of sampling, validity appropriate to the method being used, reflexivity and clear distinction between data and interpretation.

The results sections from each included study [apart from one Doctor of Philosophy (Ph.D.)] thesis were extracted from portable document format files and entered into NVivo (QSR International, Warrington, UK) as text documents.[24] We used online translation for one paper in Danish. This unconventional approach appeared to generate reasonable approximations of the original meaning and avoided the expense and delay of professional translators; this was balanced against the possibility of losing some meaning in translation.

The Ph.D. thesis[24] was read through with the other papers, but not extracted and coded until nearer the end of the process. The thesis was useful as a way of checking for gaps or absences in the data as a whole, but it was too dense and, in places, of less immediate relevance to warrant full extraction.

Synthesis

Clinical effectiveness data

Our detailed narrative synthesis explored the methodology and reported outcomes of included studies. Key study characteristics, patient outcomes and quality assessment were tabulated to provide clear summaries of the included studies. The clinical and statistical heterogeneity of the accumulated evidence was assessed. Differences between studies were discussed in the text and the potential impact of these differences on outcomes was explored. The results were interpreted in the context of the quality of the individual studies.

As anticipated, the available data were too heterogeneous for quantitative synthesis.

Cost-effectiveness data

The findings of the systematic review of full economic evaluations were summarised in a narrative synthesis.

Qualitative data

The qualitative studies were synthesised using meta-ethnography, an approach which searches each primary study and systematically extracts key findings and interpretations.[25,26] These data are then compared using a constant comparison method, which categorises key concepts to look for overlapping themes in order to enable linking of material. Each finding is subsequently assessed for similarity or difference to the other studies, and the goal is to develop, in an iterative manner, this reciprocal translation. Ultimately, new lines of argument can be developed which go beyond the data contained within the original studies.

The focus of the analysis was on themes and ideas relating directly to the provision of intravenous chemotherapy with particular reference to treatment location, rather than the experience of having cancer treatments per se.

Each results section was read closely on multiple occasions and coded line by line using participants' words where possible. Initially, codes were tagged according to the setting (e.g. code 'prefer to go home after treatment' was linked to 'outpatient setting'). Subsequent readings of the texts and resultant codes led to the reworking of the coding framework into key elements rather than distinguishing by treatment location. Codes were collapsed where possible and a process of diagramming used to explore links and interactions between the key lines of argument and categories.

Results

The electronic database searches identified 4260 references. A further 12 references were found by Google searches or by checking reference lists of included randomised trials and relevant systematic reviews. After screening titles and abstracts, full copies of 245 papers were assessed for inclusion in the review. *Figure 1* illustrates the flow of studies through the review process. Fourteen references were of papers related to another reference already included. Sixty-seven eligible studies were identified. Nine of the 25 comparative studies (10 RCTs and 15 non-randomised studies) fully evaluated in the review undertook concurrent full economic evaluations; these were evaluated separately in the review to enable a more detailed assessment. The 42 studies of single-settings are listed in *Appendix 2*. We identified a larger than expected number of comparative studies, and so we evaluated only those single-setting studies which might usefully add to the synthesis of the comparative studies. Consequently, single-setting studies were used only to inform the

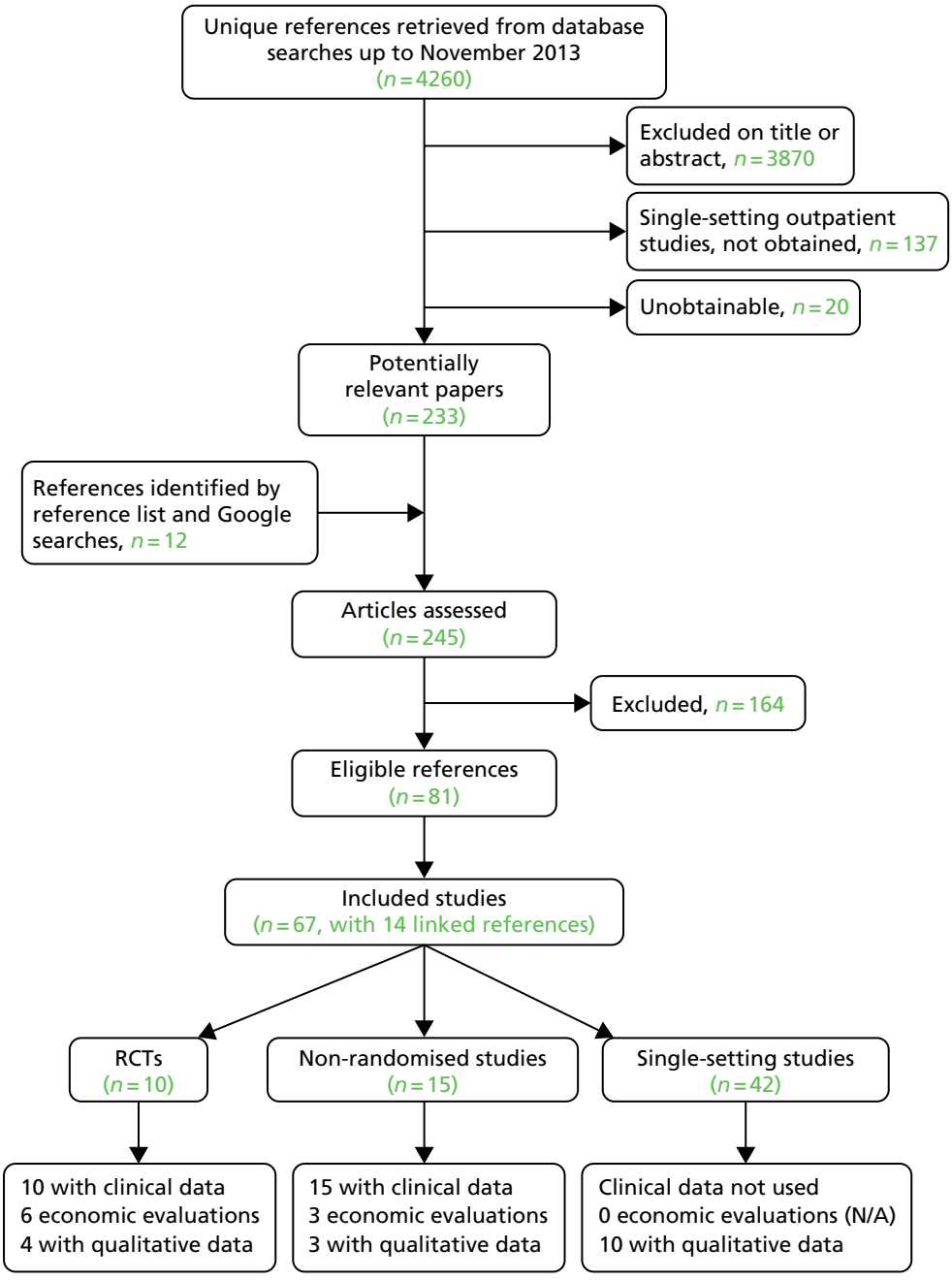

FIGURE 1 Flow chart of study selection. N/A, not applicable.

evaluation of qualitative data on patient, relative or caregiver experience of intravenous chemotherapy (see *Chapter 3*, *Results, Qualitative studies*). As we anticipated there to be a large number of single-setting outpatient studies, we ordered full papers only for studies that appeared likely to report qualitative data.

The following sections present a detailed breakdown of the results of the RCTs, non-randomised studies and economic evaluations. For each study design, study characteristics, risk of bias or quality assessment and results are presented.

Clinical effectiveness studies

Randomised trials

Study characteristics

Ten randomised trials investigated the effect of setting for patients receiving intravenous chemotherapy (*Table 1*). Six trials used a crossover design (where participants act as their own controls, and typically receive all interventions in succession). Three trials used a parallel design (where participants typically receive

TABLE 1 Summary of randomised trials included in the review

Study	Country	Sample size	Recruitment rate[a]	Setting			Outcomes
				Home	Community	Outpatient	
Corrie *et al.* 2013 (OUTREACH)[4]	England	97P	1.7	✓	✓	✓	Quality of life, anxiety, depression, health status, costs, satisfaction, serious adverse events
[b]Chen and Hasuimi 1999[27]	Japan	10P	NP	✓		✓	Quality of life, anxiety, nursing time
[b]Christiansen *et al.* 2011[28]	Denmark	51C	1.4	✓		✓	Quality of life, adverse effects, time spent receiving chemotherapy, preference, costs
Pace *et al.* 2009[29]	England	42C	3.2		✓	✓	Preference, anxiety, depression, safety, resources
Hall and Lloyd 2008[30]	England	15P	2.5	✓		✓	Experience and satisfaction, costs
King *et al.* 2000[31]	Australia	74C	1.5	✓		✓	Preferences and strength of preference, satisfaction, unmet need, quality of life, costs
Rischin *et al.* 2000[32]	Australia	25C	1.8	✓		✓	Preference, satisfaction, complications, costs
Stevens *et al.* 2006[33]	Canada	29C	NP	✓		✓	Quality of life, social/ psychological interactions, adverse events, costs
Remonnay *et al.* 2002[34]	France	52C	1.6	✓		✓	Satisfaction, costs, quality of life, anxiety
Borras *et al.* 2001[35]	Spain	87P	6.7	✓		✓	Toxicity, withdrawals, health-care resources, quality of life, satisfaction, Karnofsky Index

C, crossover design; NP, not possible; P, parallel-group design.
a Number recruited per centre, per month (estimated using the total number of patients randomised, the number of centres and the recruitment periods, except when NP).
b Studies reported only as a conference abstract.

only one intervention). One study reported only as an abstract appeared to use parallel groups and incorporated elements of a crossover design.[27] Most studies were reported as full published papers; two were reported only as conference abstracts.[27,28] Studies were published between 1999 and 2013. Three studies were conducted in the UK (England),[4,29,30] two were conducted in Australia,[31,32] and one study was conducted in each of Canada,[33] Denmark,[28] France,[34] Japan[27] and Spain.[35]

Eight studies[27,28,30–35] compared chemotherapy in the home setting with chemotherapy in a hospital outpatient setting. One study[29] compared a community setting with a hospital outpatient setting. One study[4] was a three-armed trial that compared home, community and outpatient settings. Setting details were generally not well reported; for example, aspects such as the number of nurses per patient, the degree of access to parking, and facility details were only occasionally provided. The two community settings studies assessed treatment delivered in GP surgeries and community outreach centres.[4,29] Treatment durations were often not stated explicitly or were expressed in terms of cycles; however, most studies reported chemotherapy durations ranging between approximately 2 and 8 months.

All of the trials except Stevens *et al.*[33] studied adults, with reported mean (or median) ages ranging from 57 years to 64 years. Around half of the studies were of mixed populations; patients with colon, breast, and pancreatic cancer were the most frequently studied. Studies were also conducted solely in populations with ovarian,[27] colon[28] or breast cancer.[30] The study in children was of a population with acute lymphoblastic leukaemia.[33]

The treatment intention was not always reported. Where reported it varied both within and across studies, with chemotherapy administered with either palliative or curative intent (sometimes as an adjuvant treatment). Few studies reported details on where chemotherapy drugs were prepared: in two trials drugs were prepared in the hospital pharmacy[4,29] and in one trial a community pharmacy was used.[33] Full study characteristics are reported in *Appendix 3*.

Recruitment and participation

In total, 482 participants were randomised across 10 trials. Sample sizes ranged from 10 to 97. Six studies reported a target sample size; three of these achieved or exceeded their small recruitment targets of 30 or fewer patients. Three studies did not achieve their targets: in one study a target of 20 patients was not reached (reasons unclear); one study was terminated early when 52 of a targeted 160 participants had been randomised,[34] because a large majority preferred the home setting; and the largest included study (OUTREACH) was stopped owing to the poor recruitment rate when 97 of a targeted 390 participants had been randomised (the decision was made on the advice of the independent data monitoring committee).[4] Despite this early termination, the OUTREACH trial rate of recruitment (estimated at around 1.7 patients per month per centre) was similar to the estimates for many other trials (rates ranging from 1.4 to 2.5 patients per month per centre), except for the Borras *et al.*[35] trial (around 6.7 patients per month/ per centre) and the Pace *et al.*[29] trial (around 3.2 patients per month per centre) (see *Table 1* for details).

Five of the nine trials where the outpatient setting was the standard care setting (the only routinely available setting) reported details of eligible patients who were not randomised. Between them, these five trials randomised 294 participants, but 100 eligible patients chose not to participate for setting-related reasons. Generally, these participants withdrew from the trial to revert to standard practice (which was their preferred setting). In one trial home chemotherapy was already an option before the trial began – and eligible patients had to be registered on the 'chemotherapy in the home program'.[32] In this study several patients chose not to participate because they wanted only home treatment. These data highlight the inherent bias (in terms of the types of population recruited) often encountered in trials that evaluate settings (see *Chapter 6*, *Limitations of the evidence and of the review* for more discussion of this point).

No consistent trends were found in the setting-related reasons for participants who withdrew or dropped out of trials (some studies reported limited details or none at all).

Risk of bias

Results of the risk of bias assessments are presented in *Appendix 4*. Even though only the OUTREACH trial clearly reported on both the sequence generation and allocation concealment methods,[4] most studies can be judged as being at a low risk of selection bias overall. This is largely because treatment groups had similar characteristics at baseline, a factor which was mainly a result of the use of a crossover design.

All studies were judged to be at high risk of *performance bias*; study participants and personnel will have been aware of which setting had been allocated, and avoidance of such bias is impossible. Similarly, results for the subjective patient-reported outcomes, such as quality of life and satisfaction, were judged to be at high or unclear risk of bias in all studies. Conversely, the risk of detection bias was judged low for studies reporting adverse events because they are mostly not subjective outcomes.

In four of the 10 trials the risk of *attrition bias* was judged to be low. There were insufficient details for the remaining six trials; accordingly, these trials were judged to be at an unclear risk. Four trials were found to be at a low risk of *reporting bias*, two were at a high risk of bias owing to missing results (or result detail), and in the remaining trials the risk was unclear.

Of the six crossover trials, only three clearly reported using appropriate statistical analyses. In three crossover trials the use of a crossover design appeared questionable, because of the number of patients withdrawing or dropping out because of disease progression.

Results and synthesis of randomised clinical effectiveness trials

Quality of life

Seven of the 10 randomised trials reported that they evaluated some measure of quality of life; actual result data were available for only four trials (see *Table 1*). There were no statistically significant differences in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30 items) (EORTC QLQ-C30) self-rated quality of life between any settings (home vs. outpatient;[4,28,35] home vs. GP, outpatient vs. GP[4]). Both home and outpatient settings were associated with statistically significant better results for the EORTC QLQ-30 Emotional Function outcome than in the GP surgery setting in the OUTREACH trial; there were no statistically significant differences between home and hospital settings.[4,35]

One trial used Functional Living Index Cancer (FLIC) scores as a measure of quality of life and found that setting (home vs. outpatient) had no effect on either total FLIC scores or any of the seven dimension scores.[31] The remaining trial studied 23 children using the Paediatric Oncology Quality of Life Survey (POQOLS).[33] It found statistically significant improvement associated with the home setting, compared with the outpatient setting, in terms of sensitivity to restrictions in physical functioning and the ability to maintain a normal physical routine. There were no statistically significant differences between the settings in terms of emotional distress and reaction to current medical treatment.

Clinical and psychological outcomes

Two trials reported results for EORTC QLQ-C30 self-rated health (see *Table 1*).[4,35] Both suggested that there was no difference between the home and outpatient settings. One trial compared GP and outpatient settings and GP and home settings and reported no statistically significant differences. The other study evaluated Karnofsky Index scores and reported identical scores for the home and outpatient settings.

Two trials evaluated participants using the Hospital Anxiety and Depression Scale (HADS).[4,29] Results from one trial suggested that higher levels of both anxiety and depression were associated with the GP setting, compared with the home or outpatient settings, but the results were statistically significant only for the GP versus outpatient comparison (for depression). There was little indication of any meaningful differences between the home and hospital settings. The other trial did not report any data, but stated that there were no significant differences between the community hospital and outpatient settings for both anxiety and depression.

Satisfaction and preferences

Five trials reported quantitative results for satisfaction (and related outcomes). Specific outcomes varied between studies (see *Table 1*). Two trials reported statistically significant results suggesting satisfaction benefits in terms of nursing care for the home and community settings, compared with the outpatient setting.[29,35] The largest study (OUTREACH) that compared home, GP surgery and outpatient settings in the UK reported that 78% of participants were satisfied with their treatment setting, regardless of location.[4] An Australian trial reported that significantly more patients found the outpatient setting more depressing than the home setting, although no significant differences were found for patient needs.[31] Other studies suggested no differences between groups in terms of global satisfaction,[29] or doctor-care outcomes.[35]

Five trials reported quantitative results for preferences, but only one of these trials evaluated strength of preference.[31] In the four trials where patients experienced two settings (because a crossover design was used) between 70% and 95% of patients preferred the home setting,[31,32,34] and 97% preferred a community outreach setting,[29] when compared with the outpatient setting. One trial stopped recruiting participants early owing to the strong preferences expressed for home treatment.[34]

Results from the study that considered strength of preference suggested that preferences were not very strong. It found that 34% of the participants who preferred home treatment changed their preference to outpatient treatment if home treatment was to involve waiting an extra hour, and that 27% of participants who preferred outpatient treatment changed their preference to home treatment if faced with an extra hour of waiting.[31] These results suggest that for some patients time is more important than setting. This trial was the only study to consider the issue of recruitment bias. The authors performed an additional analysis of patient preference by also including the 13 patients who chose not to participate in the trial for setting-related reasons, which they interpreted as a preference for the outpatient setting; similarly, this analysis also included the eight patients who chose not to receive home treatment after experiencing outpatient treatment (see *Appendix 3*). The results indicated that the proportion of patients who preferred home care to outpatient care was 48%.

Safety

Six trials reported on adverse events (see *Table 1*). Four trials provided some assessment of whether adverse events were related to setting (e.g. in one trial a nurse was unable to cannulate an outreach patient, who was consequently treated at the cancer centre).[4,29,32,33] They found no evidence to suggest significant differences existed between settings for any type of adverse event. Two studies evaluated only toxicity and also found no differences between settings.[28,35]

Full result details for all outcomes are presented in *Appendix 5*.

Non-randomised studies

Study characteristics

Fifteen non-randomised, comparative studies investigated the effect of setting for patients receiving intravenous chemotherapy; they were reported between 1989 and 2013 (*Table 2*).[24,36–49] Several studies were not easy to identify or access: four were reported only as conference abstracts,[42,44,47,48] one was only available as a Ph.D. thesis,[24] one was an unpublished internal report[36] and one was only available as an online report.[37] Five studies took place in England,[24,36,39,44,46] four in the USA,[42,43,47,48] two in Denmark[38,41] and one each in Wales,[40] Australia,[45] Canada[37] and France.[49]

In three studies,[24,39,41] the only review-relevant outcomes were qualitative (see *Results*, *Qualitative studies*). In the remaining 12 studies, eight compared the home and outpatient settings,[38,42–46,48,49] two compared community settings with outpatient settings,[37,47] one compared home with community settings[40] and one compared all three types of settings.[36] Population sizes were not always clearly reported, but ranged from 14 to around 2800 patients (more than half of the studies were of fewer than 100 patients). Most studies were of mixed populations; most patients had colorectal cancer, breast cancer or lung cancer. Mean ages ranged from

TABLE 2 Summary of the non-randomised studies included in the review

Study	Country	Sample size	Setting			Outcomes
			Home	Community	Outpatient	
Taylor 2008[24]	England	≈ 140	✓		✓	Qualitative data on provision of care at home from health professionals and patients
NHS Bristol 2010[36]	England	848	✓	✓	✓	Patient experience
Pong *et al.* 2000[37]	Canada	435		✓	✓	Self-reported health status, costs, satisfaction; reasons for choosing setting
Hansson *et al.* 2013[38]	Denmark	75	✓		✓	Patient- and parent-reported health-related quality of life, psychological impact on family, costs
Mitchell 2011[39]	England	20		✓	✓	Patient experience (qualitative), satisfaction, costs
Barker 2006[40]	Wales	14	✓	✓		Toxicity, satisfaction
Frølund 2011[41]	Denmark	6	✓		✓	Qualitative data on experiences of chemotherapy
[a]Grusenmeyer *et al.* 1996[42]	USA	NR	✓		✓	Costs, satisfaction
Herth 1989[43]	USA	80	✓		✓	Hope, coping
[a]Ingleby *et al.* 1999[44]	England	25	✓		✓	Costs
Lowenthal *et al.* 1996[45]	Australia	179	✓		✓	Safety, costs, resource use
Payne 1992[46]	England	53	✓		✓	Quality of life, Karnofsky performance
[a]Satram-Hoang and Reyes 2011[47]	USA	≈ 2800[b]		✓	✓	Time to treatment initiation, duration of treatment, number of cycles delivered, compliance
[a]Souadjian *et al.* 1992[48]	USA	Unclear	✓		✓	Costs, complications, quality of life, preference
Vergnenègre *et al.* 2006[49]	France	20	✓		✓	Adverse events, costs

NR, not reported.
a Studies reported only as a conference abstract. For one comparative study the design was unclear and only a conference abstract was available.[42]
b This is an estimate, as the total population of 3690 patients included 25% who received only rituximab.

50 years to 75 years, where reported. One study was in children with leukaemia or lymphoma and was the only study which indicated where the chemotherapy drugs were prepared; this study also clearly reported setting details (e.g. home care was provided by one or two nurses, depending on the tasks involved).[38] In other studies the setting details were not generally well reported; exceptions were descriptions of a community mobile chemotherapy unit,[39] and community oncology clinics.[37] Full study characteristics are reported in *Appendix 7*.

Risk of bias

Table 3 details the results of the risk of bias assessment of the non-randomised studies. Most studies were judged to be at a high or unclear risk of bias due to confounding. Although four studies did consider the effect of confounders in their study design and/or analysis plan, they did not investigate all the likely

TABLE 3 Risk of bias from confounding in non-randomised studies

Study	1. How were the groups formed?	2. Were the effects of any confounders taken into consideration during the design and/or statistical analysis stages?	3. What methods were used to control for confounders?	4. Were the data on the measured confounders recorded precisely enough?	5. Were any key confounders not controlled for?	Risk of bias from confounding
Lowenthal *et al.* 1996[45]	Oncologist decision as to which patients were offered a choice (based on having satisfactory home circumstances, and type of chemotherapy)	No	N/A	N/A	N/A	Likely to be low risk, as complications (requiring hospital admission) was the only clinically relevant outcome (unlikely to be affected by confounding)
Payne 1992[46]	Oncologist preference	Yes, diagnostic category, Karnofsky score and age were found not to be related to several quality-of-life variables	Stratified analyses for age. Stepwise multiple regression for Karnofsky score. Unclear for diagnostic category	Yes	Yes, stage of cancer. The authors acknowledged that patients who were more severely ill were more likely to be treated in the outpatient setting. Illness severity was not assessed	High
Herth 1989[43]	Non-random, convenience sample	Yes, stage of disease, age and extent of illness were considered	Matching for stage of disease. No details provided for age and extent of illness, just that they 'were not identified as confounding variables'	Yes	Yes, type of cancer, type of chemotherapy, performance status, and quality of life were not considered	High
Satram-Hoang and Reyes 2011[47]	Selection of retrospective cohorts from a database	It appeared so, but the study was only reported as an abstract so details were limited	Stratification and ANOVA	Unclear	Unclear	Unclear
Souadjian *et al.* 1992[48]	Unclear	Not reported – reported only as an abstract	N/A	N/A	N/A	Unclear

continued

TABLE 3 Risk of bias from confounding in non-randomised studies (*continued*)

Study	1. How were the groups formed?	2. Were the effects of any confounders taken into consideration during the design and/or statistical analysis stages?	3. What methods were used to control for confounders?	4. Were the data on the measured confounders recorded precisely enough?	5. Were any key confounders not controlled for?	Risk of bias from confounding
Hansson *et al.* 2013[38]	Based on distance from home to hospital. Historical controls were also used for outpatient setting	Yes, age, diagnosis, gender and time since diagnosis	Multiple linear regression	Unclear whether or not categories were used for 'age', and 'time since diagnosis' (rather than treating them as continuous variables)	Yes, stage of cancer, type of chemotherapy, quality of life and distance from hospital	High
Pong *et al.* 2000[37]	Retrospective random selection of patients from a database	No	N/A	N/A	N/A	High
Barker 2006[40]	Unclear	No	N/A	N/A	N/A	High[a]
NHS Bristol 2010[36]	Patient choice	No	N/A	N/A	N/A	High
Vergnenègre *et al.* 2006[49]	Unclear (beyond home eligibility criteria)	Not reported	N/A	N/A	N/A	Likely to be low risk since incidence of grade III or IV toxicity was the only outcome of interest, unlikely to be affected by confounding

ANOVA, analysis of variance; N/A, not applicable.
a Although adverse events were the only outcomes evaluated numerically, the ones assessed could have been affected by confounding (nausea, skin changes, lethargy and diarrhoea). Assessments were not performed for five studies: in one study there were no clinically-relevant outcomes (only costs reported),[44] three studies reported qualitative data (which are subject to a different type of quality assessment)[24,39,41] and in one study the design was unclear and only a conference abstract was available.[42]

confounders. The two studies which were given a low-risk judgement both reported adverse events as their only review-relevant clinical outcome; the types of adverse event assessed were unlikely to have been affected by any confounding factors in the populations studied.

Non-randomised study results

Three studies evaluated quality of life but their results did little to augment the RCT evidence: two studies were small, with a high risk that confounding would affect the reliability of their results; and one study was reported only as an abstract (making it difficult to interpret the results).[38,46,48] There were similar issues for the four studies of patient satisfaction.[37,39,40,42] One study included 435 patients but they were selected retrospectively, with no consideration made for confounding factors; and the study was in Canada, where the travel time and distances are different from those likely to be encountered in the UK.[37]

Only one of the four studies which had a safety outcome yielded informative results;[45] this Australian study reported that complications in the home setting were rare, although no comparative data were reported for the outpatient setting for this particular outcome. Two of the three other studies that looked at safety had very small sample sizes,[40,49] and the other was only reported as an abstract.[48] Three studies that looked at qualitative patient experience are discussed in *Results*, *Qualitative studies*.

Only one comparative study looked at the issue of treatment compliance in any detail.[47] It was conducted in the USA and studied approximately 2800 follicular lymphoma patients receiving chemotherapy [with or without rituximab (Mabthera, Roche)]. The study concluded that patients treated in the outpatient setting tended to have longer times to treatment initiation and fewer cycles across all regimens, and were less likely to receive a compliant dosing schedule than patients treated in a community clinic setting. However, the reliability of these conclusions was unclear as the study was only reported as an abstract (the risk of bias due to confounding was unclear). The results for all the non-randomised studies are presented in *Appendix 5*.

Cost data

Fourteen comparative studies reported costs as an outcome (see *Tables 1* and *2*). Cost data were recorded only to help inform the decision modelling part of the report and are presented in *Appendix 6*.

Clinical results evidence summary

The included studies revealed inherent difficulties in conducting randomised trials of chemotherapy settings. Even trials that were designed appropriately to minimise avoidable biases faced problems not only of patient accrual but also of recruiting a population to enable an unbiased evaluation of the settings. These seemingly unavoidable selection biases might be expected to produce results that favour home (or community) settings. Even so, there was little evidence of clinically relevant differences between settings in terms of quality of life and clinical and psychological outcomes. The only potentially meaningful differences were seen for some patient satisfaction and preference outcomes. However, strength of preference was studied in only one trial, with preferences appearing not to be strong in around one-third of patients. The limited safety evidence available suggested there were no differences between settings.

The non-randomised studies added little to the randomised trial evidence (although community settings were more frequently studied). The main limitations were the small populations and the high risk that study results were biased due to confounding.

Cost-effectiveness studies

Study characteristics

Nine economic evaluations published between 1996 and 2013 met the criteria for inclusion. The key characteristics, methods and results for the nine studies are summarised in *Table 4*. Details of patient characteristics and treatment regimens can also be found in *Table 4*. All nine evaluations also met the inclusion criteria and have been assessed independently as comparative studies.

TABLE 4 Summary of economic evaluation studies

Study characteristics	Main analytical approaches	Primary outcomes and health-related quality of life	Resource use	Cost analysis
Rischin *et al.* 2000[32] (full paper) Country: Australia Settings: home; hospital outpatient	Economic evaluation alongside a RCT (crossover, $n = 25$ recruited, $n = 20$ evaluated) Analysis: CEA (CCA) Perspective: hospital Time horizon: two chemotherapy cycles	Patient preference and satisfaction All patients preferred remaining treatment at home. 0% reported concerns with home treatment, 20% had concerns with hospital. 90% felt that there were advantages to home, 5% hospital	No resource use data reported Cost categories: nurse time and travel, vehicle costs, one meal in hospital. Unclear if drug costs included	Price year NR Home associated with average increased cost of AUS$83 per treatment vs. hospital (95% CI AU$46 to AU$120; $p = 0.0002$) First treatment AUS$57 more expensive than second treatment on average (95% CI AUS$20 to AUS$94, $p = 0.0044$)
King *et al.* 2000[31] (full paper) Country: Australia Settings: home; hospital outpatient	Economic evaluation alongside a RCT (crossover, $n = 74$ recruited, $n = 40$ evaluated) Analysis: CEA (CCA) Perspective: health service Time horizon: 4 months	Patient preference and strength 73% (95% CI 59% to 86%; $p = 0.008$) preferred home. Strength of preference was low. Preference dropped to 48% (95% CI 35% to 60%; $p = 0.61$) when accounting for preferences of withdrawn patients (p-value testing if = 50%). No apparent differences in quality of life (FLIC score) between settings	No resource use data reported Cost categories: nurse cost, travel time, vehicles, equipment, cost of capital and overhead costs. Individual category costs reported	Price year NR Net additional cost of home vs. hospital: AUS$68.81. Additional cost attributed to extra nurse time Cost of new chemotherapy ward = AUS$70,581. Home chemotherapy less expensive per treatment than a new ward used with up to 50% ward capacity. New ward less expensive above 50% ward capacity
Lowenthal 1996 *et al.*[45] (full paper) Country: Australia Settings: home (included workplaces, GP offices, day-care centres); hospital outpatient	Analysis based on a retrospective non-randomised audit ($n = 184$ recruited, $n = 179$ evaluated) Analysis: CEA (CMA) Perspective: hospital Time horizon: 5 years for safety, 1 year for costs	Safety: single setting (number of major complications at home only) One major complication among visits to 179 patients. Assumed this would be at least as safe as in the hospital (no data for hospital) The authors appeared to assume equal efficacy between settings	Reported number of visits, duration, travel and preparation time Cost categories: labour, travel, hospital resources, pharmaceuticals and overheads (drug costs assumed the same). Individual cost category costs reported	Price year: 1994 AUS ($) Cost per home chemotherapy treatment: AUS$49.93. Hospital: AUS$116.00 Annual cost to deliver 345 chemotherapy treatments and additional services for 65 patients in the hospital (extending hours): AUS$38,207. Home: AUS$45,767

Study characteristics	Main analytical approaches	Primary outcomes and health-related quality of life	Resource use	Cost analysis
Corrie *et al.* 2013[4] (full paper) Additional data from personal communication with author Country: UK Settings: home; GP surgery; community (GP + home); hospital outpatient	Economic evaluation alongside a RCT ($n = 97$ recruited, $n = 57$ evaluated) Analysis: CUA Perspective: NHS Time horizon: 12 weeks	EORTC QLQ-C30 QoL Emotional Function domain: No difference for community vs. hospital. Home vs. GP: 15.2, 95% CI 1.3 to 29.1; $p = 0.033$ (favoured home). GP vs. hospital: –16.6, 95% CI –31.4 to –1.9; $p = 0.028$ (favoured hospital) EQ-5D: No significant differences. Unadjusted mean (SD) QALY home: 0.165 (0.036); GP: 0.191 (0.04); hospital: 0.174 (0.034). Based on 14 hospital patients, 15 GP, 19 home (complete-case analysis) Patient preference: 57% of hospital patients preferred future treatment in hospital, 81% GP, 90% home	Resource use data collected from nurse diaries and Client Service Receipt Inventory Unit costs from PSSRU (included salaries and overheads) Cost categories: inpatient, outpatient, day hospital, A&E visits, community care, medication, and nurse diaries contact. Nurse travel (not patient) included	Price year: 2010 GBP Home: £2139 (SD £1590); GP: £2497 (SD £1759) Hospital: £2221 (SD £1831) ICER GP vs. hospital = £16,235/QALY gained
Pace *et al.* 2009[29] (full paper) Country: UK Settings: community hospital; hospital outpatient	Economic evaluation alongside a RCT (crossover, $n = 42$ recruited, $n = 31$ evaluated) Analysis: CEA (CCA) Perspective: NHS and patient Time horizon: completion of treatment	Patient preference and satisfaction 30/31 (97%) patients chose to receive remaining cycles of treatment in the community hospital and would have preferred to receive all their chemotherapy there	Service-related resource Average round-trip mileage from main hospital to community centres = 24.2 miles Total time of 104 minutes for each treatment Two nurses for each treatment Patient-related resource Average patient distance from community clinic = 10.25 miles vs. 19 miles to hospital	Price year NR Service costs: Average cost of round-trip = £12.83 per clinic session. Opportunity cost of travel for each nurse (based on £29,538 salary) was £32.08 (£64.16 for two nurses, £384.96 for six cycles = marginal cost of clinic) Patient costs: Mean cost of travel and parking for patients to outreach = £4.85/treatment vs. £8.77 for hospital. Including private car and public transport cost, average cost to attend outreach = £8.07 vs. £14.99 to hospital

continued

TABLE 4 Summary of economic evaluation studies (*continued*)

Study characteristics	Main analytical approaches	Primary outcomes and health-related quality of life	Resource use	Cost analysis
Stevens *et al.* 2006[33] (full paper) Country: Canada Settings: home; hospital outpatient Paediatric population	Economic evaluation alongside a RCT (crossover, $n = 29$ recruited, $n = 23$ evaluated) Analysis: CEA (CCA) Perspective: societal Time horizon: 1 year	POQOLS QoL questionnaire Factor 1 (normal physical routine): switching to home led to an improvement, switching to hospital led to a worsening (–10.5 for home vs. +5.2 for hospital $p = 0.023$) Factors 2 and 3 (emotion and reaction): no significant differences due to crossover. Comparison using end of 6-month data; children at home had significantly higher emotional distress than at hospital ($p = 0.043$) Child Behaviour Checklist No significant differences	No resource use data reported Parents provided resource use data for physician/care provider visits, medications/supplies, babysitting, travel and productivity losses. Cash transfer effects were assessed (unemployment insurance, workman's compensation, mother's allowance) Costs excluded health professionals who administered chemotherapy and drug costs	Price year NR Total societal costs were reported for each setting at three time points. At 1 year (last time point): home ($n = 13$), median CAD$851 (range $147–8726); hospital ($n = 9$), median CAD$1050 (range $29–10,278); $p = 0.95$ Home had higher costs at baseline, and lower costs at 6 and 12 months. No evidence that costs were affected by location of treatment The difference between family costs associated with home vs. hospital was not significant ($p = 0.79$) (no family costs reported)
Vergnenègre *et al.* 2006[49] Country: France Settings: home; hospital outpatient	Analysis based on non-randomised comparative study ($n = 20$ recruited, $n = 20$ evaluated) Analysis: CEA (CCA) Perspective: health service Time horizon: NR	Adverse events Home: two adverse events in 24 cycles Outpatient: seven adverse events in 30 cycles Not statistically significant difference ($p = 0.27$)	Resource use for home Home visit nurse time = 130 minutes (€0.25/minute) Administrative costs = 30 minutes (€0.19/minute) Co-ordination costs = 30 minutes (€0.40/minute) Hospital costs were reported as aggregates with/without comorbidities. Home treatment costs included chemotherapeutic drugs, nursing, co-ordination, administration, disposables, transportation, GP visits and non-chemotherapeutic drugs	Price year NR Average cost per cycle was €2829.51 (95% CI €2560.74 to €3147.02) for hospital infusion, €2372.50 (95% CI €1962.75 to €2792.88) for home-based care (–16.15%). Difference was €–457.01 by cycle (95% CI –€919.74 to €26.82) in favour of home. Real costs by injection for home was €484.42 (95% CI €424.18 to €540.32) vs. a fee of €699.89 (95% CI €643.64 to €750.23) (–30.79%)[a]

Study characteristics	Main analytical approaches	Primary outcomes and health-related quality of life	Resource use	Cost analysis
Remonnay *et al.* 2002[34] (full paper) Country: France Settings: home (managed by an external association – Soins et Santé); hospital outpatient	Economic evaluation alongside a RCT (crossover, $n = 52$ recruited, $n = 42$ evaluated) Analysis: CEA (CCA) Perspective: societal Time horizon: four treatments	Patient satisfaction 95% of first 52 patients preferred chemotherapy at home, recruitment discontinued after that point	No resource use data reported Costs categories: personnel, medication, transport, laundering and overhead	Price year: 1998 USD Marginal cost (i.e. excluding overhead costs) for one treatment home vs. hospital: US$232.5 vs. US$157; $p < 0.0001$ Average cost (including overheads): $252.6 vs. $277.3; $p = 0.002$ Category costs reported in paper
Hansson *et al.* 2013[38] (full paper) Country: Denmark Settings: home; hospital outpatient Paediatric population	Economic evaluation alongside a non-RCT ($n = 89$ recruited, $n = 75$ evaluated) Analysis: CEA (CCA) Perspective: hospital Time horizon: 2 years	PedsQL scale Trend towards higher home-care QoL Parent Proxy Cancer Module Significantly better physical health and less worry for children in the home-care group Child Self-Reported Cancer Module; Family Impact Module No significant differences	No resource use data reported Cost of home-care service included nurse wages, car hire, fuel, parking, new nurse uniforms, nursing bags, equipment, safe storage and hospital overhead costs (administration)	Price year NR Hospital charge for home visit: US$597 Hospital visit: US$600 Disaggregated costs for categories of home-care cost reported in Danish krone in linked study

A&E, accident and emergency; CCA, cost–consequence analysis; CEA, cost-effectiveness analysis; CI, confidence interval; CMA, cost-minimisation analysis; CUA, cost–utility analysis; EQ-5D, European Quality of Life-5 Dimensions; ICER, incremental cost-effectiveness ratio; NR, not reported; PedsQL, Paediatric Quality of Life; PSSRU, Personal and Social Services Research Unit; QALY, quality-adjusted life-year; QoL, quality of life; SD, standard deviation.

a Confidence level not given in paper.

CCA is a type of CEA where costs and outcomes are reported separately, with no combination into a ratio statistic; CEA is an analysis where monetary costs and clinical outcomes in natural units are reported. CEAs often have final results reported as ratios of incremental costs to incremental benefits; CMA is a type of CEA where equivalence of outcomes has been assumed, and therefore only costs are considered for decision-making; CUA is an economic evaluation where costs and patient quality of life, measured through preference-based utility scores, are compared. CUAs often use ratio statistics final results.

Three of the evaluations were conducted in Australia,[31,32,45] two in the UK (England),[4,29] two in France[34,49] and one in each of Canada[33] and Denmark.[38] Most studies assessed adult populations; two studies assessed paediatric populations.[33,38] Six evaluations were conducted alongside RCTs, two alongside non-randomised controlled studies,[38,49] and one was conducted as part of a retrospective audit.[45] Most studies did not conduct a full incremental analysis i.e. to produce [incremental cost-effectiveness ratios (ICERs)], but instead reported cost and health outcomes separately. Costs and outcomes were generally assessed over a short time horizon (1 year or under).

All of the non-UK studies compared treatment delivered in the home with treatment delivered in a hospital outpatient setting.[31–34,38,45,49] The two UK studies included community settings: Pace *et al.*[29] compared treatment delivered in a community hospital setting with treatment delivered in a hospital outpatient setting; and OUTREACH[4] compared home, GP surgery and hospital outpatient settings. None of the economic evaluations assessed the delivery of chemotherapy by mobile bus units. One study assessed the delivery of home chemotherapy by a third-party charity organisation.[34] In all other studies it was implied that home/community care was delivered by the health service.

As highlighted in the clinical study sections, most studies assessed mixed populations with various cancer types, including breast cancer, colon cancer, lung cancer, gastrointestinal cancer, lymphoma, pancreatic cancer and leukaemia. One study assessed only patients with acute lymphoblastic leukaemia.[33] An array of treatment regimens was used for a mixture of curative, supportive and palliative intent. The populations appeared to be heterogeneous in terms of disease severity.

The nine evaluations conducted alongside clinical studies recruited a total of 593 patients and 487 participants were evaluated in the concurrent economic evaluations. Most of these participants were evaluated in the two non-randomised studies; 179 patients were evaluated in the retrospective audit[45] and 75 were evaluated in the controlled study.[38] The six evaluations made concurrently with RCTs were based on small data sets:[4,29,31–34] the largest study (OUTREACH)[4] had complete primary outcome data (EORTC QLQ-C30 Emotional Function subdomain) on only 57 participants across three treatment arms/settings. *Chapter 6* contains an overview of recruitment and participation within the RCTs (see *Limitations of the evidence and of the review*). The number of participants informing the concurrent cost-effectiveness analysis is presented in *Table 4*, alongside other study characteristics and findings.

Economic quality assessment

The Drummond checklist was used to assess methods and reporting in the nine included economic evaluations.[20] Clinical studies undertaken alongside the economic evaluations were assessed for risk of bias as part of the quality evaluation of comparative studies (see *Table 3* and *Appendix 4*). All of the evaluations suffered from limitations, as highlighted by the checklist. Many did not undertake appropriate data collection and/or sensitivity analyses. Seven of the nine studies reported no data on resource use outcomes, which significantly reduces the transparency and transferability of the results. Five studies reported disaggregated costs (costs for each of the included cost categories rather than a total cost only), but the usefulness of such costs in terms of informing potential UK NHS cost estimates is limited without resource use data. Reporting of methods used to derive cost and resource use outcomes was limited and this made the validity of the cost estimates unclear. Most studies failed to report the price year or any cost adjustments applied. None of the studies conducted an adequate analysis of the potential impact of uncertainty on the results; all three studies that included sensitivity analyses were limited in scope. Most studies failed to consider the generalisability of their results. Full results for the quality assessment can be found in *Table 5*.

Overall, the studies were deemed to be of low or uncertain quality due to small sample sizes; limited reporting on resource use, costs and methodology; and lack of robust sensitivity analyses. There is likely to be significant uncertainty around the cost-effectiveness results.

TABLE 5 Drummond checklist economic evaluation quality assessment

Item	Response by study								
	Rischin *et al.* 2000[32]	King *et al.* 2000[31]	Lowenthal *et al.* 1996[45]	Pace *et al.* 2009[29]	Stevens *et al.* 2006[33]	Vergnenègre *et al.* 2006[49]	Remonnay *et al.* 2002[34]	Hansson *et al.* 2013[38]	Corrie *et al.* 2013[4]
Study design									
1. The research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	Yes	Yes	No	Yes	No	Yes	No	No
4. The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. The alternatives being compared are clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. The form of economic evaluation used is stated	No	No	No	Yes	No	No	Yes	No	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Data collection									
8. The source(s) of effectiveness estimates used are stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

continued

TABLE 5 Drummond checklist economic evaluation quality assessment (*continued*)

Item	Response by study								
	Rischin *et al.* 2000[32]	King *et al.* 2000[31]	Lowenthal *et al.* 1996[45]	Pace *et al.* 2009[29]	Stevens *et al.* 2006[33]	Vergnenègre *et al.* 2006[49]	Remonnay *et al.* 2002[34]	Hansson *et al.* 2013[38]	Corrie *et al.* 2013[4]
12. Methods to value health states and other benefits are stated	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes
13. Details of the subjects from whom valuations were obtained are given	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No
14. Productivity changes (if included) are reported separately	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A
15. The relevance of productivity changes to the study question is discussed	N/A	N/A	N/A	No	Yes	Yes	N/A	N/A	N/A
16. Quantities of resources are reported separately from their unit costs	No	No	Yes	Yes	No	Partially	No	No	No
17. Methods for the estimation of quantities and unit costs are described	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
18. Currency and price data are recorded	No	No	No	No	No	No	Yes	No	No
19. Details of currency of price adjustments for inflation or currency conversion are given	No	No	No	No	No	No	No	No	No
20. Details of any model used are given	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
21. The choice of model used and the key parameters on which it is based are justified	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Analysis and interpretation of results									
22. Time horizon of costs and benefits is stated	Unclear	Yes	Yes	Unclear	Yes	No	No	Unclear	Yes
23. The discount rate(s) is stated	No	N/A	N/A	No	N/A	N/A	No	No	No
24. The choice of rate(s) is justified	Unclear	Yes	Yes	No	Yes	No	Unclear	Unclear	Yes

Item	Response by study								
	Rischin *et al.* 2000[32]	King *et al.* 2000[31]	Lowenthal *et al.* 1996[45]	Pace *et al.* 2009[29]	Stevens *et al.* 2006[33]	Vergnenègre *et al.* 2006[49]	Remonnay *et al.* 2002[34]	Hansson *et al.* 2013[38]	Corrie *et al.* 2013[4]
25. An explanation is given if costs or benefits are not discounted	No	No	No	No	No	No	No	No	No
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	Yes	N/A	No	Yes	Yes	Yes	Yes	Yes
27. The approach to sensitivity analysis is given	N/A	Yes	N/A	N/A	N/A	Yes	Yes	N/A	Yes
28. The choice of variables for sensitivity analysis is justified	N/A	No	N/A	N/A	N/A	Yes	No	N/A	No
29. The ranges over which the variables are varied are stated	N/A	Yes	N/A	N/A	N/A	Yes	Yes	N/A	N/A
30. Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Partially
31. Incremental analysis is reported	No	No	No	No	No	No	Yes	No	Partially
32. Major outcomes are presented in a disaggregated as well as aggregated form	No	Yes	Yes	Yes	No	Partially	Yes	N/A	No
33. The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
34. Conclusions follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35. Conclusions are accompanied by the appropriate caveats	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
36. Generalisability issues are addressed	No	No	Yes	No	Yes	No	Yes	Yes	No

N/A, not applicable.

Economic study results

Health outcomes

Several health outcomes were assessed in the nine economic evaluations: EORTC QLQ-C30, FLIC scores, safety and adverse events, patient satisfaction and patient preferences. It was unclear why only one economic evaluation reported quality-adjusted life-year (QALY) outcomes when these would better facilitate modelling.

There was no robust evidence of any meaningful between-setting differences for most health outcomes (EORTC QLQ-C30, FLIC scores, safety and global satisfaction). There was less than robust evidence that emotional functioning, anxiety and depression were improved in the home and outpatient settings compared with a GP surgery (OUTREACH)[4] and that satisfaction was higher in the home than in the outpatient setting in terms of nursing care and the depressive nature of the setting.[29,31] Evidence in the child population was limited. Children's quality of life was improved in the home setting, compared with an outpatient setting.[33] A full description of these health outcome results, as measured in the trials, is presented in *Results*, *Clinical effectiveness studies*.

OUTREACH measured patient utility across outpatient, home and community (GP practice) settings in a UK population using the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.[4] The study recruited 97 participants: 57 patients provided data for analysis of the primary end point EORTC QLQ-C30 and 48 provided EQ-5D utility scores; there were no details of why nine patients provided data on the primary outcome but not for EQ-5D.

The OUTREACH publication[4] reported total QALYs gained but not baseline values. Mean differences from baseline over a 12-week period showed that the community setting produced the largest change [0.191 QALYs; standard deviation (SD) 0.04 QALYs], followed by hospital outpatient (0.174 QALYs; SD 0.034 QALYs), and home (0.165 QALYs; SD 0.053 QALYs).

The OUTREACH authors provided us with an analysis of the difference in mean differences adjusted for baseline EQ-5D utility values. With adjustment for differences in baseline QALYs, hospital outpatient chemotherapy was found to produce the most QALYs and was used as the reference for other treatment settings. Compared with the outpatient setting, the community setting (GP practice) had a mean difference of –0.009 ($p = 0.0471$) and the home setting had a mean difference of –0.010 ($p = 0.374$) (P McCrone, Centre for the Economics of Mental and Physical Health, Institute of Psychiatry, King's College London, personal communication). These data implied that patients treated in a GP/community and hospital settings had a lower health-related quality of life at baseline, suggesting that they might have been in a poorer health state than participants who were treated at home.

There were significant limitations with these data. In particular, they were based on a small number of patients (19 or fewer in each treatment arm) and both the adjusted and unadjusted QALY results were subject to significant uncertainty. None of the results achieved statistical significance and it would be inappropriate to draw definitive conclusions on the basis of these data.

Resource use and costs

Reporting for resource use and costs across the nine economic evaluations was variable. Cost categories and perspectives were similarly inconsistent. These inconsistencies in resource use and perspectives across the economic evaluations make it difficult to ascertain any objective trend in favour of one treatment setting over another.

Only two studies reported resource use, an Australian study[45] and a UK study,[29] but details were limited to travel and labour. Both studies reported resource use for nurse travel to community or home settings.[29,45] Pace *et al.*[29] reported resource use for patient travel, in addition to nurse travel, to a community outreach

site, and the number of nurses needed to deliver the service in the community setting. Lowenthal *et al.*[45] reported hours spent on delivering treatment as well as time spent travelling and preparing treatments.

Costs across the included evaluations varied widely. Most studies were from non-UK settings, which can limit the generalisability of resource use and cost data to the NHS and reduced their usefulness in informing a de novo model for this review. Costs and resource use across the countries vary greatly owing to differences in health-care delivery systems and differences in the prices paid for services.

One of the non-UK studies, Remonnay *et al.*,[34] compared chemotherapy administered in an outpatient setting with chemotherapy administered at home by a charitable organisation. The care concept has relevance to the UK as several examples of chemotherapy delivered in the community as part of a partnership between a charitable organisation and hospital have emerged in recent years.[50–53] In the Remonnay *et al.* study,[34] the charitable organisation paid higher costs for chemotherapy drugs than the outpatient facility (25% to 121% higher) because of differences in purchasing methods. In sensitivity analysis, drug costs were made equivalent for home administration, which led to home chemotherapy being less costly than outpatient administration. This was primarily due to large overhead costs in the outpatient setting. The study was generally well reported, but did not report resource use, which limits transferability to a UK setting. The authors were contacted for further information, but no response was received.

The review identified two UK economic evaluations, both of which, owing to scope and reporting, were of limited usefulness in informing a de novo model. The study by Pace *et al.*[29] was concerned only with travel time and did not consider other health-care resources and costs that might differ between settings. The OUTREACH trial[4] presented only total costs for each treatment arm in their published paper, with no breakdown of the costs within each intervention arm. Correspondence with the authors led to additional cost data being provided. These data were broad cost categories including inpatient and outpatient costs, day hospital costs, accident and emergency (A&E) visits, non-cancer medications and nurse diary contacts. The review team identified some discrepancies in these data. Queries were raised with the authors, but were not resolved. In brief, for some cost categories the data appeared to be resource use with no total cost provided, for other categories the data were total costs with no resource use data, and for some categories it was not clear which were being presented.

Overall, the evidence on resource utilisation and costs was extremely limited. Data sets were small, results were inconsistent and there was a great deal of between-study heterogeneity for patient characteristics and methodology; these limit the generalisability of the results.

Economic evidence summary

Quality across the economic evaluations was variable, and overall should be considered poor. Biases in the clinical study, the level of reporting on resource use and associated unit costs, and the lack of health-related quality-of-life outcomes were major limitations. Poor reporting of resource use and the use of different perspectives across the different settings made the results difficult to compare. Several economic evaluations used patient preference as an outcome measure, rather than health-related quality-of-life outcomes, which are more widely used to inform decision-making.[29,32,34,45,54] High levels of uncertainty make it difficult to ascertain whether or not costs or outcomes differ between settings.

Qualitative studies

Overview of study characteristics and quality

Seventeen qualitative or mixed-methods studies were included in this review (published between 1984 and 2012).[4,24,29,30,32,39,41,51,55–64] The studies were conducted in Canada (four[55–57,60]), the USA (one[59]), the UK (nine[4,24,29,30,39,51,62,63]), Denmark (two[41,61]), Iceland (one[64]) and Australia (one[32]). UK studies were in England (six[4,24,29,30,39,62]) and one in each of Wales,[51] Northern Ireland[63] and Scotland.[58] *Table 6* displays a summary of the included study characteristics. *Appendix 8* gives full details of the extracted data. *Table 7*

TABLE 6 Summary of qualitative study characteristics

			Perspectives presented within the data (patients included both children and adults)			Contexts discussed			
Study	Linked to trial?	Country	Patients	Carers/partners/parents	Health-care professionals	Home	Community	Outpatient	Data collection
Bakker *et al.* 2001[57]	No	Canada	✓ $n = 28$				✓	✓	Purposive sample Interviews
Butler 1984[59]	No	California (USA)	✓ $n = ?$			✓		✓	Sample unclear Follow-up interviews
Corrie *et al.* 2012[4]	Yes (RCT)	England (UK)	✓ $n = 11$		✓ $n = 15$	✓	✓	✓	Purposive sample Interviews
Crisp 2010[60]	Yes (pilot non-RCT)	Alberta (Canada)	✓ $n = 10$			✓		✓	Convenience sample Interviews
Frølund 2011[41]	Yes (case series)	Denmark	✓ $n = 6$			✓		✓	All case series included Interviews
Hall and Lloyd 2008[30]	Yes (RCT)	England (UK)	✓ $n = 15$			✓		✓	All trial patients included Interviews
Hansson 2011[61]	Yes (non-RCT)	Denmark	✓ $n = 11$[a]	✓ $n = ?$		✓		✓	Purposive sample Interviews (with families)
Hjorleifsdottir *et al.* 2008[64]	No	Iceland	✓ $n = 25$					✓	Convenience sample Interviews
Iredale *et al.* 2011[51]	No	Wales (UK)	✓ $n = 6?$				✓	✓	Sampling not reported Interviews
Kelly *et al.* 2004[62]	No	England (UK)	✓ $n = 5$		✓ $n = 12$	✓		✓	Targeted convenience sample Interviews
McIlfatrick *et al.* 2007[63]	No	Northern Ireland (UK)	✓ $n = 30$					✓	Convenience sample Interviews

Study	Linked to trial?	Country	Perspectives presented within the data (patients included both children and adults)			Contexts discussed			Data collection
			Patients	Carers/partners/parents	Health-care professionals	Home	Community	Outpatient	
Mitchell 2011[39]	No	England (UK)	✓ $n = 20$	✓ $n = ?$			✓	✓	Convenience sample Interviews
Pace *et al.* 2009[29]	Yes (RCT)	England (UK)	✓ $n = 11$				✓	✓	All patients in trial Open-ended questionnaire item
Rischin *et al.* 2000[32]	Yes (RCT)	Australia	✓ $n = 20$			✓		✓	All patients in trial Open-ended items in questionnaire
Smith and Campbell 2004[58]	No	Scotland (UK)			✓ $n = 19$		✓	✓	Purposive sample Telephone interviews
Stevens *et al.* 2004[56]	Yes (RCT)	Canada			✓ $n = 33$	✓		✓	Purposive sample Interviews
Stevens *et al.* 2006[55]	Yes (RCT)	Canada	✓ $n = 14$[a]	✓ $n = 24$		✓		✓	Convenience sample Interviews
Taylor 2008[24]	No	England (UK)	✓ $n = 9$	✓ $n = 2$	✓ $n \approx 130$	✓		✓	Convenience and purposive sample Focus groups, open-ended questionnaires and interviews

a Children.

TABLE 7 Summary of qualitative study quality

Study	Author's position/ reflexivity	Sampling	Data collection	Data analysis	Validity/validation	Participants' voice	Data vs. interpretation	Transferability/ generalisability
Bakker *et al.* 2001[57]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Butler 1984[59]	No	Unclear	Unclear	Unclear	Unclear	Yes	No	No
Corrie *et al.* 2012[4]	No	Yes	Unclear	Unclear	No	Yes	Unclear	Yes
Crisp 2010[60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Frølund 2011[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hall and Lloyd 2008[30]	No	Yes	Unclear	Unclear	No	Yes	Yes	No
Hansson 2011[61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hjorleifsdottir *et al.* 2008[64]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No
Iredale *et al.* 2011[51]	Unclear	Unclear – not reported	Yes	Unclear	No	Yes	Unclear	No
Kelly *et al.* 2004[62]	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
McIlfatrick *et al.* 2007[63]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mitchell 2011[39]	Yes (partial)	Yes	Yes	Yes	Yes	Yes	Yes	No
Pace *et al.* 2009[29]	No	Yes	Yes	No	No	Unclear	Unclear	No
Rischin *et al.* 2000[32]	No	Yes	Yes	No	No	Unclear	Unclear	No
Smith and Campbell 2004[58]	No	Unclear	Yes	Yes	Yes	Yes	Yes	No
Stevens *et al.* 2004[56]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stevens *et al.* 2006[55]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Taylor 2008[24]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes

provides summary quality assessment results. Stevens *et al.* 2006[55] and Stevens *et al.* 2004[56] are separate publications from the same study, where one paper reported on health-care professional views and the other focused on the experiences of the children and their parents; these two publications have been kept separate for clarity and, therefore, there were 18 sources of data contributing to the synthesis.

Participant views represented include chemotherapy patients (16 studies;[4,24,29,30,32,39,41,51,55,57,59–64] two included children[55,61]); carers/partners or children's parents (four studies[24,39,55,61]); and health-care professionals (five studies[4,24,56,58,62]). The study contexts varied, with half the studies taking place within a clinical study. Participants often spoke comparatively about their experiences based on current and prior treatment received or given.

Six papers contributed data on community provision of intravenous chemotherapy.[4,29,39,51,57,58] Eleven papers contributed data on the home setting[4,24,30,32,41,55,56,59–61] and one paper was a theoretical discussion of a proposed service.[62] All 18 papers included discussion of outpatient settings and two studies focused exclusively on this.[63,64] The OUTREACH study contributed data on all three settings.[4]

As discussed in the summary of the quantitative studies (see *Chapter 6*, *Strengths of the review, Clinical effectiveness studies*) study populations are likely to reflect a limited and biased perspective given the nature of the research. All papers dealing with community or home chemotherapy were based around new services, pilots or trials, which implies that the provision may be particularly high quality. It was rare to see any indications of problems with the new services. There was one comment about the chance of the community chemotherapy bus being cancelled but the patient noted that this never occurred. One Canadian study mentioned problems with drug deliveries.[55] There were no studies discussing new community cancer suites or outpatient chemotherapy suites; these facilities tend to offer integrated care in light and airy spaces designed for comfort.[65,66]

Almost all patients expressed a preference for treatment location, with varying degrees of strength. The few patients who did not seem to mind about location were clear that the treatment was a necessary inconvenience regardless of the place it occurred.

It is worth noting that although Smith and Campbell[58] was a discussion around a proposed community service, the views and comments from participants were essentially the same as those given by patients who had received community chemotherapy in other studies. This suggests that focus group work may be a useful preamble to setting up new services, as both patients and health professionals are likely to identify any potential barriers and benefits, enabling pre-emptive action.

Fifteen studies[4,24,30,39,41,51,55–58,60–64] used interviews to gather data (one study used telephone interviews[58]), and two used open-ended questions on a questionnaire.[29,32] One study collected data through focus groups, open-ended questionnaires and telephone interviews.[24]

Most papers did not clearly identify the author's position, or appear to engage substantially with reflexivity. That is, they did not appear to consider the impact of the researcher on the data collection and analysis. Four papers at least partly addressed these issues including considering the potential impact of the author on the data collection and analyses process.[39,41,60,61] Other papers either did not clearly identify the researcher who collected and analysed the data or did not discuss the implications where the researcher was a cancer nurse.[30]

The most common form of sampling was based on convenience; fewer studies used purposive sampling and three studies included all patients who participated in the trial or pilot.[29,30,32] Information on participation rates was scantly reported across the studies making it difficult to draw any general conclusions. In some studies, staff delivering care to study participants were responsible for recruitment or suggesting participation; this may have contributed some bias.

Study methodology was reported infrequently. Analyses were most commonly labelled as content analysis (five studies[55,56,58,61,64]) or thematic (four studies[24,30,51,62]). Two studies used framework,[4,57] two used phenomenology,[39,41] one used the constant comparative method[60] and one used narrative analysis.[63] Three studies did not report their methods of analysis.[29,32,59]

Validation and the consideration of validity can be a problematic topic within qualitative research. Ten out of 18 studies[39,41,55–58,60,61,63,64] in this group reported using some form of validation. This included peer discussion, independent coding by more than one researcher and discussion of preliminary findings. Most studies provided clear quotations from the participants and emphasised the primacy of the interviewee's voices. Thirteen out of 18 studies[24,30,39,41,55–58,60–64] drew clear distinctions between collected data and researcher interpretation. Transferability and generalisability were discussed in some detail by nine studies.

Synthesis

Overall, the data were grouped under three main lines of argument (*Table 8*). Two were relatively self-contained: one addressed issues around perceived cost and barriers to service use, while the second addressed satisfaction with treatment experience and provision.

The third line of argument was more substantial than the other two, and more clearly relates to specific issues of the setting for intravenous chemotherapy. The decisions made by patients, carers and family members were focused on maintaining normality in everyday life. Compromises were required to balance competing factors and patients' location preferences reflected their individual situations.

The three main lines of argument are not entirely independent; where links were obvious these have been noted in the descriptive text that follows.

TABLE 8 Overview of main lines of argument

	Key lines of argument		
	Barriers to service provision	**Satisfaction with intravenous chemotherapy**	**Making compromises to maintain normality**
Example codes	Staff personal safety concerns	Communication	Medical expertise
	Reluctant to treat	Information provision	Safety
	Patient safety	Understanding information	Additional procedures and tests
	Lack of professional support	Privacy	Keeping cancer out of the home
	Capacity concerns	'KFC'-style treatment	Shared experiences with other patients
	Cost of the service (patient and staff views)	Rapport and relationship with health professionals	Time: travel time and costs
	Lack of communication between health professionals	Security	Time: waiting for treatment
			Time: to spend on other activities
			Anxiety
			Fatigue and energy
			Identity
			Control

KFC, Kentucky Fried Chicken.

Line of argument: perceived barriers

Most data within this concept were contributed by health professionals (oncologists and nurses of varying grades) rather than by the patients (*Figure 2*).

Several patients cast doubt on the cost-effectiveness of home chemotherapy, even where they had reported positive experiences:

> *It's just not cost-effective we're going into a period of austerity, you know cut backs and all the rest of it [patient]*
>
> *It's crazy [wife]*
>
> *It doesn't make any sense to me [patient]*
>
> *Patient and wife*[39]

Comments such as this suggest that patients may not take advantage of an offered service where they feel it is a waste of resources, even if they would find it personally useful.

The health professionals from Kelly *et al.*'s study[62] raised issues of the costs in setting up the service and numbers of patients who could be treated, commenting that it was very difficult to accurately estimate costs for a new service. The consultant questioned whether or not offering home chemotherapy would simply mean that the spare capacity in the outpatient ward would be swallowed up by new demands. Similar views were expressed by health-care professionals in the study by Taylor.[24]

> *You can't take one bit out and leave a gap and not expect it to fill in very quickly. We're more like a beach than a building.*
>
> *Consultant*[62]

Health professionals from the Stevens *et al.* study[55] commented that additional administrative tasks required for home visits were time-consuming. While actual visit time was relatively brief, preparation calls, such as checking drug deliveries or telephoning for blood test results, were described as 'frustrating'.[55]

FIGURE 2 Line of argument: barriers.

Both consultants and nurses raised concerns around the personal safety of health professionals travelling alone to patients' homes.[4,24]

> *If something went wrong you are on your own, you've got no back-up whatsoever if anything happened.*
>
> *Chemotherapy nurse*[4]

One consultant highlighted that working in settings other than outpatient wards meant a potential lack of peer support and guidance for staff.

> *The nurses will be doing it in isolation, they can't ask anyone to come and have a look and it's quite nice often to run things past someone else.*
>
> *Oncologist*[4]

The potential for lack of communication or inconsistent treatment between settings was also flagged up by health-care professionals in Stevens *et al.*[56] This was seen as a factor that could damage trust between outpatient and community staff teams, but clarifying responsibilities and increasing communication would reduce this.

> *Many hospital HPs [health professionals] indicated that inconsistent interaction with the child and family was somewhat distressing and that they would prefer regular updates on the child's progress . . . The HPs also emphasised the need for treatment procedures to be consistent in the home and hospital.*[56]

Line of argument: satisfaction

There was a cluster of codes around satisfaction with the treatment overall including facilities and staff (*Figure 3*). This seemed to sit outside the trade-off being made by patients to maintain normality and is likely to reflect concerns and experiences about NHS treatment in general. Data here include elements specific to home and community treatment.

FIGURE 3 Line of argument: satisfaction. KFC, Kentucky Fried Chicken.

As mentioned earlier, all of these data relate to new community or home services, and to pre-existing outpatient settings. None of these studies looked at the newer, purpose-built chemotherapy suites, and so it is unsurprising that many of the comments about physical facilities reflected unfavourably on the outpatient environment. Mobile buses in particular were described as being relaxed, warm, calm and very unlike a busy hospital.[51] This has clear links into the largest line of argument around maintaining normality: such facilities offer a middle ground between the comfort of home and the barren hospital.

Communication Good communication (e.g. between community chemotherapy settings and the main cancer hospitals) was cited as a factor in increased confidence for patients receiving treatment in other locations. The faxes, e-mails or telephone calls indicated that local staff were in contact with, and supported by, the larger cancer care team. This category links into medical expertise versus normality as discussed in the third line of argument.

> *The staff at the [regional] cancer center phoned the nurse here and told her what she was to give me and she had everything ready for me the next day. I feel confident that if I called her, she would have the answer . . .*
>
> *Patient*[57]

This communication also balanced out some of the potential disadvantages in a less technologically developed community setting.

> *Maybe you don't have the technology that you would have at the big cancer centers . . . but I believe that in the smaller clinics the comfort you find with the communication compensates for some of the loss in technology.*
>
> *Patient*[57]

In contrast, poor communication around waiting times and making appointments was felt to be a particular problem in outpatient settings. This is explored in more detail in the following section. Patients were clear about not holding the nurses responsible but complained about the organisational aspects and systems.

> *You couldn't fault the staff it's just that it doesn't seem to be very logistically organised at all . . . All I can say about it is it just needs leadership. . . . since the new clinic [has been built] the appointments are worse, far worse.*
>
> *Patient*[39]

Aspects such as the physical layout of the outpatient units, the use of temporary facilities that are still required after 10 years, and logistical difficulties in scheduling appointments all tended to lead to frustration on the part of both health-care professionals and patients. As Kelly *et al.*[62] reported, staff working in the chemotherapy unit experienced regular difficulties when trying to communicate between these different sites.

> *There's just so many links in the chain that almost inevitably one breaks down. So it's set up to be very difficult to manage.*
>
> *Nurse*[62]

Information There was often a large amount of information to take in before and after chemotherapy treatment. One study indicated that patients struggled to access the desired information from their doctors in the outpatient setting which reduced control and increased anxiety.[63] Data from Crisp,[60] and Hall and Lloyd[30] suggested that patients found it easier to understand the information in the home setting rather than in an outpatient clinic. Patients commented that they felt more able to ask questions of the nurses

when at home and that the extra time made it easier to ask about the niggling concerns that might be missed in an appointment with the doctor. In one example, the nurse telephoned the patient later on to answer a specific query, indicating a high level of ongoing communication.

> *I was able to really talk to the nurses and the nurses had a lot more time with me. It was one on one time. So I got way more information from my treatment at home meetings than with my doctor.*
>
> *Patient*[60]

Privacy The mobile bus services were mentioned in relation to privacy, both positively and negatively. Iredale *et al.*[51] reported that patients felt it was like having a private room, whereas Mitchell's[39] participants reported that the close proximity of the treatment chairs meant very little privacy in relation to physical aspects of treatment. However, this was not perceived to be an unresolvable problem once, for example, patients *'get used to knowing what to wear'*.

Home settings were associated with increased privacy, which patients valued in relation to the side effects of the chemotherapy. Crisp reported patients preferring to use 'their own bathrooms for vomiting or diarrhoea or taking steps to make intravenous insertion easier'.[60] Home chemotherapy was described as more private also because no-one was listening in on patients' conversations.[30]

Rapport with health professionals and individuality A mixture of experiences was reported across settings in relation to forming good relationships with the health professionals. There was no clear indication that one setting resulted in better rapport than any of the others and some patients were particularly keen to highlight the excellent care they received from both outpatient and community or home chemotherapy staff.

Hospital staff appeared to be under more pressure than their home or community counterparts; however, they were still delivering excellent care in most of the accounts included in this synthesis. Patients valued the human contact as highly as the actual treatment itself.

> *This also included the importance of receiving treatment, which was given in a warm and sensitive way, and caring encounters were seen as closely intertwined with the treatment itself.*
>
> *Author interpretation*[64]

In one of the studies which included interviews with children, they commented that they liked the hospital sessions particularly because of getting to see their favourite regular nurses.[55]

Community chemotherapy settings were most often described as personal, friendly and more relaxed than outpatient clinics, which allowed more time to ask questions. This included the input of the mobile bus driver, who made patients a cup of tea and showed them where to wait for treatment.[39,51]

The patient who said that they preferred outpatient over community treatment cited *'the gloomy décor and lack of atmosphere at the outreach location'*,[29] which may suggest that physical environments are influential in decision-making. Alternatively, this may highlight the particularly subjective nature of such experiences and judgements. It was not clear from the data how such preferences interacted with travel time and waiting times.

Consistency of nursing staff was mentioned most often in relation to chemotherapy delivered at home. Having the same nursing team for each visit combined with the feeling of having their *'undivided attention'* to increase satisfaction levels.[30,41,60,61] Patients did not have to repeat themselves to multiple new nurses and there was an improved understanding of their circumstances, which led to an easier exchange of information. Seeing the same well-qualified and punctual nurses was particularly important for parents

in the Hansson *et al.* study, who felt this increased security. The children enjoyed showing their home-care nurses around the home.[61]

> *I like to have the same nurse who is my main nurse, it is the relationship with my nurse, she knows everything about me and I know a lot about her, this is like a friendship.*
>
> *Paediatric patient*[64]

In contrast, Frølund reported that patients felt that it was more important to be treated by an experienced nurse than to see the same nurse on every visit. This was not reflected in other data but remains a valid comment on treatment preferences.[41]

Despite these generally positive comments, one couple reported that they felt that the home-care nurse had less time for questions and discussion than the hospital nurses.[67] The only negative comments from health-care professionals reflected the reduced contact with parents and children who were having treatment at home. While the hospital nurses valued having the extra time to spend with other patients, they worried about how the home treatment children were coping with their treatments.[56]

Line of argument: compromise to maintain normality

The degree to which patients expressed a preference about where they received chemotherapy appears to depend on which location offered the best possible compromise between a range of factors which are discussed in the following pages. The balancing act can be seen as between factors that favoured outpatient treatment and those that favoured an alternative to outpatient. That is, there was no clear distinction between home and community settings (mobile or other location), but a collection of factors which might sway a patient towards preferring non-outpatient treatment.

Themes *pushing* towards outpatient treatment Themes which seemed to push patients and carers/parents towards outpatient treatment included medical expertise, safety, scheduling non-chemotherapy treatments, keeping cancer out of the home and shared experiences with other patients (*Figure 4*).

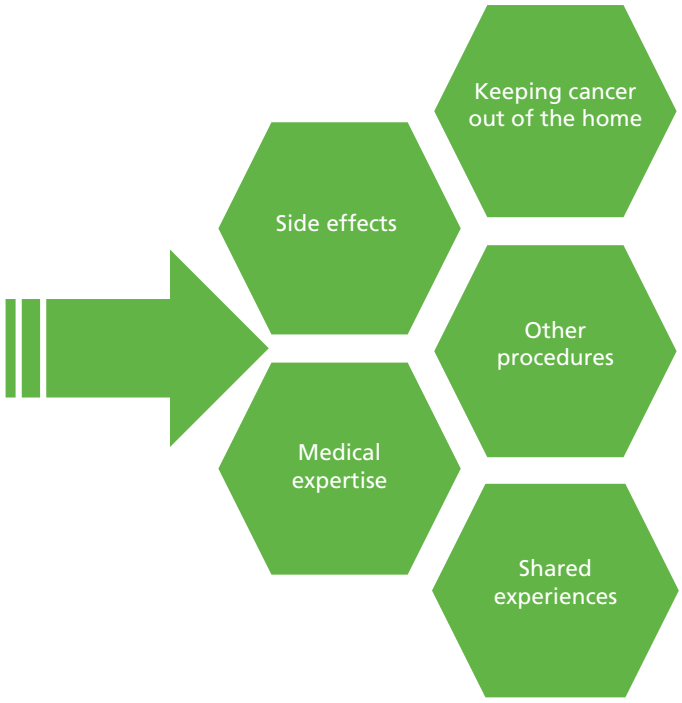

FIGURE 4 Factors pushing patients towards outpatient treatment.

Medical expertise and safety concerns Medical expertise and safety was mentioned in all of the included study results and was clearly an important factor when patients and health-care professionals were thinking about preferred treatment locations. Community clinics were generally characterised as being less technologically advanced, although this was described as a 'small disadvantage' rather than a major concern in one study.[57]

There was a mixture of experiences across those studies where patients experienced more than one setting. As described earlier, for some patients the evidence of clear communication and support between community and outpatient settings was sufficient reassurance,[57] while for others they preferred to be treated in hospital with immediate access to the expertise.[4,39,64] These patients tended to have already experienced outpatient care and were unwilling to try a service such as the mobile chemotherapy unit even when assured it would be delivered by the same nurse team.

> *. . . it was exactly the same treatment as Cheltenham, . . . the reason I didn't opt for it, and it isn't really logical, . . . was simply because I was confident with the treatment I had at Cheltenham and it was the feeling of not wanting to put that at risk.*
>
> *Patient*[39]

Concerns about safety and being unwilling to take chances were most strongly expressed in one study of paediatric cancer patients, although this was not consistently demonstrated in all child-related data. In Stevens *et al.* 2006,[55] some patients felt more secure in the hospital setting, particularly where there was a concern about negative reactions to the chemotherapy.

Some studies highlighted specific concerns relating to the medical equipment such as catheters, pumps and intravenous devices. Again, there was a mix of views between patients who were worried about what might happen in the home setting,[59] and those who found that it was easier to prepare for intravenous insertions in the warmth of their own home[60] and so worried less about the associated procedures.

Additional procedures and tests In all of this data set, patients still had to attend the outpatient clinics for review meetings or monitoring via blood tests or other procedures. The logistical arrangements prevented some patients from being able to have community chemotherapy owing to the need for co-ordinating tests and treatments, which resulted in disappointment.[39] In Stevens *et al.*'s Canadian study,[55] the children receiving home chemotherapy visited a local laboratory to have bloods taken while the children having outpatient treatment had bloods taken in the hospital. This caused some problems as the laboratory used venous sampling which could be more painful than the finger-stick sampling children were accustomed to from the hospital. Although this was not seen as a major disadvantage, it was an unpleasant experience which reduced the appeal of home chemotherapy treatments.[55] There was no evidence in the data that patients would prefer outpatient treatment in order to enable all of the tests and procedures to be carried out in one location or visit.

Keeping cancer out of the home For some patients and parents of children, one of the key benefits to having their chemotherapy in the outpatient unit (as opposed to at home) was the ability to keep the cancer segregated from everyday life. In these situations, being able to go home after treatment was seen as a relief and allowed the cancer to be left in the hospital.[4,56,61,63]

> *I know I sound a bit weird, but there is also the thing that if you are treating the cancer at home, then the cancer is at home.*
>
> *Patient*[4]

The fact that the chemotherapy treatment was carried out as an outpatient was also seen as helpful; being able to walk in and walk out reduced the feeling of being ill.[63] Where there were other children in the family, treatment in the hospital allowed the home to remain as a safe refuge, although treatment at home was felt in some cases to reduce sibling anxiety about the whole process.[61]

Shared experiences with other patients Opinions among the patients and families were mixed when it came to the benefits of being treated among those experiencing similar illnesses.[4,32,41,60,61,63] Health professionals were also divided in their opinions.[58,60] Positive aspects included being able to talk to other patients, which was described as cathartic.

> *You're talking to patients out in the waiting area, the person sitting beside you. Not talking in any morbid way, but you're exchanging experiences. It's a great therapy.*
>
> *Patient*[63]

It also allowed the conversation to stay within the hospital setting.

> *It's like a support group in its own. Once you do that, you don't need to talk about it outside anymore; you feel part of some kind of exclusive club.*
>
> *Patient*[63]

For some parents of children being treated with chemotherapy, being able to form relationships with other families was seen as a useful source of support.[61] One study reported that an adult patient felt that it was beneficial to see others who were worse off.[32]

These benefits were also reported in relation to community chemotherapy settings, where smaller groups of patients were often being treated simultaneously. The chance to share experiences was seen as part of the treatment.

> *When I first went in I thought well this isn't very private at all . . . actually as I sat and watched, I thought no, these people are sharing conversation with each other . . . there was a kind of bonding that went on between the patients.*
>
> *Patient*[4]

Some of the patients who had mainly received chemotherapy at home suggested that they might have preferred the chance to meet other people in the same situation, although this was not particularly strongly expressed.[30,60]

Themes *pulling* away from outpatient treatment Themes which pulled patients and carers away from outpatient treatment and towards the alternative (regardless of what form that might take) included specialist expertise, normal life, energy, travel, waiting time, identity, control, support network and anxiety about treatment. These were more broadly grouped under the idea of patients desiring control over a range of factors (*Figure 5*).

Pre-treatment anxiety Chemotherapy in the outpatient setting was frequently associated with pre-treatment anxiety, nausea and other unpleasant side effects. Four studies also reported that following a return to hospital treatment (either for routine reasons or due to the end of pilot service provision), patients experienced anxiety-related problems.[55,57,60,61]

In contrast, community chemotherapy was seen as less stressful owing to reduced travel and easier parking, while home chemotherapy was mentioned in relation to reduced treatment-related anxiety.[32,51,57,60] For one patient this was particularly pertinent as she also suffered from irritable bowel syndrome:

> *Helen suffered from Irritable Bowel Syndrome (IBS), and described her difficulties travelling back and forth to the hospital. At home, she had the luxury of using her own washroom and reported having less frequent attacks as a result of reduced anxiety.*[60]

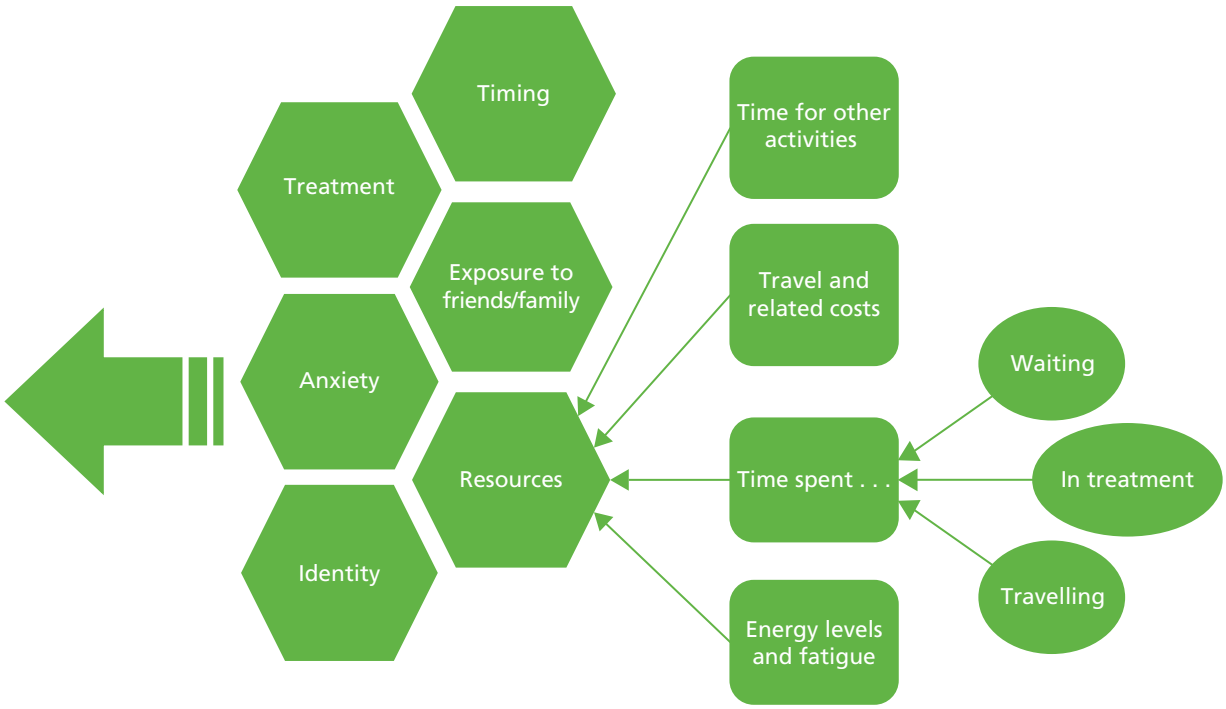

FIGURE 5 Factors pulling patients away from outpatient treatment.

Identity and control The shared experiences and contact with other patients or families in the same situation, mentioned earlier as a beneficial aspect of outpatient chemotherapy, were sometimes seen as a disadvantage.[4,41,60,61,63] Interestingly, none of the respondents mentioned these comments in relation to community settings, although they would seem to be equally applicable.

Attending the hospital and seeing others who were more or less sick than them was quite difficult for some patients. Seeing others who were more ill added to the anxiety and fear of future deterioration, and in some cases emphasised their identity as a sick person.[41,60]

> *I know that death is coming, but I don't need to be reminded of it several times a week.*
>
> *Patient*[41]

The whole experience of visiting hospital for chemotherapy was identified as potentially pulling patients back into the sick role that many were trying hard to escape from.

> *Although health care professionals strive to promote patient independence and self-care, there are still aspects of treatment that seem to pull the patient back into the traditional sick role.*
>
> *Author summary*[60]

The formation of friendships during treatment in outpatient hospital settings was discussed earlier as a positive aspect, but loss of these friends when they died was difficult. For some participants this led to a deliberate withdrawal from social contact.

> *I saw a lot of people dying, I found that very off-putting. I say to myself now, I'm not going to get friendly with anybody else, because when something happens, and then, you know, it sort of unnerves you.*
>
> *Patient*[63]

While for some patients being treated as an outpatient made it easier to keep cancer away from the home, for others being treated at home minimised the impact of the disease. This was particularly obvious in data gathered from mothers with cancer who had young children. For example, the patient below describes how the disruption to daily routines caused by outpatient treatment was more difficult than the shorter home chemotherapy appointments.

> *My husband's mom lives on Vancouver Island and she came over to help look after us and she was really worried that the kids were going to associate her with Mom being sick. Because she would only come when I was having treatments or when I needed help.*
>
> *Patient*[60]

In some situations home chemotherapy offered the chance for the children to see the benefits in reduced stress and anxiety, which improved the family experience in general, while for other parents the home treatments were more easily scheduled when children were at school, which made it easier to hide them.

> *I mean, we have such a close family. And we're so involved with each other and I think for my children to see me happy and settled is a gift for them.*
>
> *Patient*[60]

Overall, treatment at home was associated with having greater control over how much or how little other family members living either at home or elsewhere were exposed to the chemotherapy processes.

Time also influenced this theme; as one participant eloquently stated, reducing the time spent on treatment made the illness less invasive for the whole family.

> *Home care diminishes the invasion in one's life that the illness represents. It simply makes that invasion smaller: you don't feel that affected by the illness as a family, when it means 20 minutes in your own home compared to when it means 6 hours at the hospital.*
>
> *Patient*[61]

Being able to perform normal daily tasks as a result of receiving chemotherapy at home in turn reduced the impact of the disease on their identity.

> *I have a deadly cancer, I know. It is there, and it will always be there . . . Home treatment makes me feel normal . . . It helps that I can live as before I got the disease.*
>
> *Patient*[41]

Individuality In contrast to some of the positive views expressed within the qualitative synthesis (see *Line of argument: satisfaction*), seeing different doctors in the outpatient setting who were not necessarily up to speed on the case notes was described as disjointed and frustrating.[39]

This lack of individualised and tailored understanding was reflected in the comments from participants in McIlfatrick *et al.*'s study.[63] The outpatient setting was described as factory-like and dehumanising, with little chance to discuss more general concerns or the person outside their cancer treatment.

> *It's quick. It's like a KFC [Kentucky Fried Chicken] cancer ward . . . you can see they have to, with, I mean, with the amount of people that comes through. But they still try to keep a personal touch to it, but it is hard for them.*
>
> *Patient 7*[63]

Time: travel time (and costs) The time taken to travel to and from outpatient centres for chemotherapy was frequently mentioned across the included studies, in terms of duration of travel, costs for patients and carers and the energy expended.[4,29,32,39,51,55–57,60–62,64]

For most patients the journey to the hospital took considerable time, with associated parking difficulties and costs. This in itself might not have been such a problem, but when combined with the often long waits for treatment, patients were spending almost a full day on the chemotherapy treatment.[51]

These long days were particularly difficult as patients were already feeling ill, and children might be nauseous and anxious.

> *Traveling is difficult, especially when you know you're going to be sick and it's very tiring.*
>
> *Parent of paediatric patient*[57]

> *It was exhausting for the parents and the child to get up in the morning and go to the hospital and they experienced it as stressful to leave the home with a child who was plagued by nausea and vomiting.*
>
> *Author summary*[61]

Travel and parking costs were often mentioned as adding to the anxiety about chemotherapy treatment, particularly for families with children and single parents who struggled to both find the funds and take the time off work.[55,61,62] Arranging childcare when the parent was required to attend hospital for treatment incurred additional financial burdens, and in some cases significantly impacted on family life.[60]

The importance of reducing travel time lies in the ability of the patient (and their carer) to make 'better use' of this time, and money, such that they might be able to continue to work, go to school and participate in normal activities.[55,60,61]

Time: waiting for treatment Community and home chemotherapy settings benefited from reduced travel times, but participants also commented frequently and favourably on the absence of waiting to be treated. Community chemotherapy was highlighted for the short waiting time prior to treatment; patients reported that they were able to arrive just before their appointment and be seen almost immediately. This appeared to reflect a more organised system which was much appreciated by patients as it meant the total time spent travelling and being treated was perhaps 2 hours rather than the full day required for outpatient chemotherapy.

> *A typical day at the clinic is as long as a normal working day, whereas treatment at home is just over an hour.*
>
> *Patient*[41]

In Mitchell's study,[39] waiting time and travelling time were some of the most important factors in every patient's choice to have treatment on the community chemotherapy bus.

Outpatient chemotherapy accounts frequently mentioned the unpredictable nature of waiting times.[39,56,60–62,64] Health professionals also mentioned the difficulty in managing waiting times, referring to organisational factors such as drug ordering systems.

> *The way that the present service was configured contributed to this problem. For instance, delays occurred between the ordering of chemotherapy drugs and their arrival in the clinic.*[62]

Some participants commented that waiting itself was a tiring activity made more difficult by the lack of facilities or the lack of heating, which made subsequent intravenous insertion more problematic.[39,60,64]

> *The waiting room was described as uncomfortable, and having to wait there was tiring for people with little strength and sometimes in pain.*
>
> *Author summary*[64]

Despite this issue, this same patient understood and was sympathetic to the possible reasons for the unexpected delays.

Home settings generally involved no waiting time and the nurses were praised for their punctuality. The decreased waiting time in home and community settings meant that the portion of the day spent on treatment was significantly smaller, thus impacting on attempts to maintain normality. Some of the health professionals from the Stevens *et al.* study[56] commented that the increased flexibility within home chemotherapy benefited their teenage patients, but could be more stressful for the staff, who were trying to accommodate patient requests.

> *I found that we were juggling a lot. Trying to work around the teenagers' schedules because you would end up calling them to say that you were going to come to do the chemo and they would say 'Oh no I'm off to something or other tonight'.*
>
> *Nurse*[56]

Waiting and travel time somewhat naturally clustered together within the data set. McIlfatrick *et al.*'s paper[63] adds a useful aspect by highlighting that, for patients, this meant more than just travelling to and waiting for treatment.

> *Whenever you have the treatment, your life does revolve around it . . . you are marking time.*
>
> *Patient*[63]

Time: time to spend on other activities/relationships In many of the studies where home or community chemotherapy was available, patients commented favourably on being able to do things (such as bathe and eat) when they wanted rather than have those activities 'dictated by the convenience of hospital routine'.[59] The time which was freed up by not having to travel such long distances or wait as long for treatment could then be used for jobs around the house or going back to work (adult patients) or, for children, being able to continue attending school.[30,41,55,57,60]

This additional time allowed patients to stay in touch with their own personal support networks, whether these were family or friend oriented. Outpatient care was associated with the loss of these networks,[59,60] although for some patients the relationships formed with other patients might have been some compensation.

> *When patients are diagnosed with cancer, they are displaced from their homes to a contrived, heavily scheduled setting such as a hospital. Routines are lost, and the patient becomes bound by 'the system'.*
>
> *Author summary*[60]

Patients were keenly aware of having a limited amount of time to spend with friends and family, particularly in cases where the treatment was not likely to be curative. Parents valued the opportunity to spend more time with partners and children.

> *Savouring positive experiences as a family frequently becomes paramount to cancer patients and their families.*
>
> *Author summary*[59]

Home chemotherapy was most often mentioned in relation to being able to spend more of the available time with key people.

> *Time is a great opponent . . . An invincible opponent. I know that I have an incurable disease, and therefore it is very important that I can be with family and friends. For me, home treatment has given me this opportunity to a greater extent.*
>
> *Patient*[41]

Fatigue and energy Chemotherapy was universally described as a difficult process resulting in fatigue caused by both the treatment side effects and the travelling and waiting time.

> *I found even driving (to the hospital) and getting my chemo, by the time I got home, I'd have to have a nap. I found myself getting tired from it really quick.*
>
> *Patient*[60]

This was important both to patients and to their carers, who were also affected. For example, parents of children receiving chemotherapy commented on the beneficial effects of home care for their children, and also for themselves.

> *[W]ith home care the children could sleep as much as they needed . . . a great burden had been lifted from their shoulders in a period when they didn't have much energy due to their child's life-threatening disease and their lack of a normal everyday life.*
>
> *Parent of paediatric patient*[61]

Patients talked about having a finite budget of energy, with home and community chemotherapy leaving more resources for them to spend as they chose after treatment.

> *In the past I put a cross in calendar. The whole day was devoted to the treatment . . . when I receive treatment at home; I have the energy to do other activities.*
>
> *Patient*[41]

Qualitative summary

The synthesis incorporated data from 18 papers and over 450 participants including health professionals, patients (adults and children), parents, carers, siblings and partners. Most of the available data focused on experiences of outpatient and home settings for intravenous chemotherapy, with some data on community settings including mobile bus units. Overall, the quality of the included studies was moderate to good.

Maintaining normality was the important overarching theme which tied much of the data together. Across the data set, the importance of maintaining normality throughout a difficult illness/treatment was seen as key to being able to survive and look forward. Exactly what normal life constituted varied from patient to patient. Most patients were clearly making explicit trade-offs to maximise their resources (e.g. time, money or energy). Looking at the data set, it was rarely as simple as saying that one setting maintained normality and alleviated any safety-related concerns. Health professionals recognised and referred to this when talking about their patients, indicating a shared understanding.

Normality was more easily maintained when family life was minimally interrupted, the impact of cancer on daily life and family members was controllable, and patients were able to participate in activities of value. The time and energy consumed by chemotherapy underpinned much of this category: time spent travelling and waiting for treatment meant less time for normal life. The energy expended on treatment (including travel and waiting time) could leave patients unable to participate in important activities. Although treatment- and setting-related anxiety or side effects were mentioned, these seemed to be important because dealing with the anxiety, stress and nausea took up valuable time and energy.

While the outpatient settings were most often associated with increased confidence in the staff's ability to deal with adverse reactions, there was some evidence that good, visible communication between an expert centre and an outreach location could ameliorate some of the safety concerns. Based on the available data, the time and energy consumed by outpatient treatment reduces overall quality of life and this is a sufficient driver for patients to prefer alternative treatment locations. These themes were particularly evident in the accounts from patients receiving palliative treatment and from parents of children with cancer.

Chapter 4 Identifying current provision

Introduction

Based on the scoping work undertaken to facilitate this research and discussions with our advisory group, we were aware that there appeared to be variation in chemotherapy delivery practices throughout the UK. This variation was expected to include the likely existence of a variety of systems, reflecting the different challenges of large cancer centres and district hospitals, for example. Nurse-led chemotherapy is established in some centres but home delivery of chemotherapy is not widespread. Different geographic challenges exist for provision in remote and rural communities compared with more urban-based centres.[3,10] Some hospitals elect to utilise private providers to deliver services, while some elect to deliver these 'closer to home' services using their own NHS resources. To gain insight into the variation in current practice in the NHS, we undertook a survey canvassing views from relevant professionals about their experience of the delivery of home and community chemotherapy. The survey was not intended to be comprehensive; rather, it was intended to provide a general overview that would help to describe the patient pathway and inform the development of the decision model.

Methods

Owing to the likely variation in private provision and NHS provision of services, we designed two questionnaires on current provision of intravenous chemotherapy administered at home and in the community. Both were administered using an internet-based survey programme (Survey Monkey: www.surveymonkey.com) between June 2013 and September 2013. One was circulated to NHS trust organisations providing chemotherapy services and the other was sent to commercial organisations identified as providing home care or community services on behalf of the NHS.

Invitations to participate in the NHS provision questionnaire were sent via e-mail to stakeholders across England and Wales. Individuals were identified via the Cancer Network websites (where still available) and their replacement clinical groups, and through contacts provided by members of the advisory group. The survey was administered between June 2013 and September 2013. Invited participants were encouraged to disseminate the questionnaire to colleagues. Briefly, the questionnaire asked participants whether or not their hospital offered chemotherapy at home and/or in the community, how long their service had run for, who delivered it, what type of pharmacy was use and staffing details, as well as setting characteristics for the community setting. The full survey is available in *Appendix 9*.

The private provider questionnaire was sent to HaH, Calea UK Ltd, Bupa Home Healthcare, Baxter, Polar Speed Distribution Ltd, Alcura UK, Evolution Homecare Services Ltd, B. Braun Medical Ltd and MedCo. These providers were identified via the advisory group who provided contact details for the National Clinical Homecare Association, an industry body representing companies providing clinical home care services to NHS patients along with charitable and independent sectors within the UK. In brief, the survey asked whether the organisation delivered intravenous chemotherapy in the home or community setting on behalf of the NHS, what aspects of home or community chemotherapy were provided, who was involved in administering and overseeing the service, and whether or not any unpublished information was available. For organisations that provided the service, follow-up questions were sent to gather further details about provision of home- and community-based intravenous chemotherapy. The full survey is available in *Appendix 10*.

Responses

The aim of the surveys was to provide a general overview of current provision to inform this project. In the following sections we describe and summarise the main responses to the surveys. Full details of all responses to both surveys are available on request.

NHS provision survey

Respondents and services provided

We sent 65 e-mails inviting stakeholders to participate and sent a reminder e-mail to non-respondents after 2 months. Respondents were encouraged to forward the survey to other contacts; this increased the number of responses at the expense of making the percentage response unclear.

In total, 26 people from 22 organisations provided usable survey responses to the NHS survey. Sixteen of the 22 organisations were in the north of England and six were in the south. Organisations included trusts, specific hospitals and one commissioning body. Respondents were in various roles including commissioners, pharmacists, cancer nurses, oncologists, regional managers, haematologists, directors and administrators. All survey respondents were in England.

Ten organisations provided chemotherapy at home or in the community: three delivered intravenous chemotherapy only in the home, three delivered only in a community setting and four delivered treatment in both settings.

Figure 6 provides a flow chart demonstrating the services provided by respondents.

Aspects of the service and pharmacy use

Two of the seven organisations that provide chemotherapy at home indicated that the NHS delivered all aspects of the service, one failed to respond and four indicated that they used a private provider to deliver some or all of the service. Two of those using a private provider indicated that they used a hospital pharmacy for home chemotherapy; both of these deliver treatment in the home and community setting. The other two organisations which deliver in both settings were both NHS-provided services, including pharmacy.

Two of the three organisations providing treatment only in a community setting indicated that the NHS provided all aspects of the service, including hospital pharmacy, and one did not respond. *Table 9* provides service provision details for settings offered, pharmacy use and training/recruitment requirements for services in the home or community.

Staff and training necessary for administration of chemotherapy at home or in the community

Staff involved in administration of chemotherapy in the home or the community included oncologists, nurses, haematologists and pharmacists. Five organisations responded that additional training and/or additional recruitment was required for their service, two indicated that no additional training was required and three did not respond. Nurses were the focus of additional training, which included training nurses to higher certification levels, training them on how to use mobile chemotherapy units (chemotherapy bus), and lone-worker training. Three of the five organisations that indicated additional training was required delivered in both settings (two NHS and one private provider). Two organisations delivered only in a community setting using a NHS service.

Three organisations indicated that hiring additional staff was required, while two indicated that it was not and five failed to respond. All of those that indicated that they would need to hire additional staff also indicated that additional training would be required; two of these were community NHS-delivered services and the other a NHS-delivered service across both settings. The two organisations that indicated no

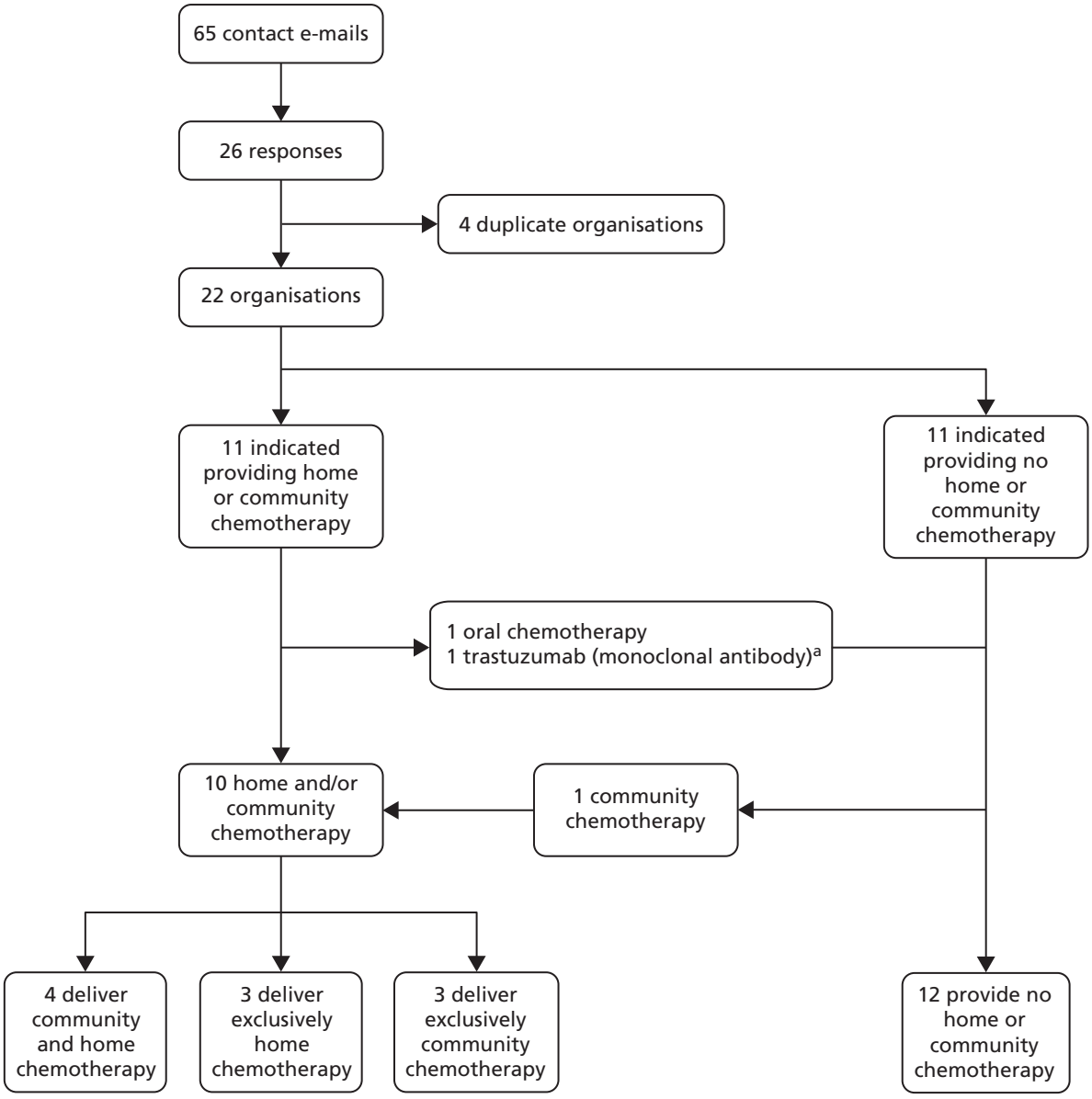

FIGURE 6 Flow chart of current NHS provision of home and community intravenous chemotherapy.
a, Herceptin®, Roche.

TABLE 9 Provision of home and community chemotherapy

	Services provided		Home services				Community services				Additional training	
Organisation identifier	Home chemotherapy	Community chemotherapy	NHS delivers all aspects of service	Private provider delivers some/all of service	Hospital pharmacy used	Private pharmacy used	NHS delivers all aspects of service	Private provider delivers some/all of service	Hospital pharmacy used	Private pharmacy used	Hire additional staff	Required additional training
1	✓	✓	✓	–	✓	–	✓	–	✓	–	NR	Yes
2	–	✓	–	–	–	–	✓	–	✓	–	Yes	Yes
3	✓	–	NR	NR	NR	NR	–	–	–	–	NR	NR
4	✓	✓	–	✓	✓	✓	–	✓	✓	✓	NR	Yes
5	✓	–	–	✓	–	✓	–	–	–	–	NR	NR
6	–	✓	–	–	–	–	✓	–	✓	–	Yes	Yes
7	✓	✓	✓	–	✓	–	✓	–	✓	–	Yes	Yes
8	✓	–	–	✓	-	✓	–	–	–	–	No	No
9	✓	✓	–	✓	✓	–	✓	–	✓	–	No	No
10	–	✓	–	–	–	–	NR	NR	NR	NR	NR	NR

–, not applicable or not delivered; NR, no response.

additional hiring also indicated no additional training requirements; both services had home services that were delivered by private providers.

The number of nurses involved in delivering intravenous chemotherapy in a home or community setting varied between organisations. Two organisations used one nurse at their community locations and three organisations used two nurses. Two organisations did not report how many nurses they used for community chemotherapy locations. The number of nurses who administered each individual treatment at home and community locations was fairly consistent. All five organisations that provided a response reported that one nurse was involved in each intravenous treatment.

The details of services provided, by whom and where, plus additional staff hiring and training requirements for each of the organisations, are presented in *Table 9*.

Eligibility for participation in home chemotherapy

Various eligibility policies were described for home chemotherapy. One of four organisations that provided home chemotherapy via a private provider reported an eligibility requirement of 'a few' cycles delivered in hospital; another reported that eligibility decisions were based on regimens; and two did not report eligibility requirements. There were few responses regarding eligibility requirements for chemotherapy; three organisations provided no response to eligibility requirements for chemotherapy at home and one reported that drug regimen suitability determined patient eligibility for chemotherapy at home.

Three of the seven organisations that provided chemotherapy at home reported that patients were referred to the service by consultants, and two indicated that consultants and specialist nurses could refer patients to the service. No other organisations provided referral details.

Three organisations provided estimates for the proportion of patients eligible for the home service and the proportion of patients accepting the service. There was a mix of proportions eligible and accepting, with some eligibility levels of $< 5\%$. Both organisations that indicated $< 5\%$ eligibility also indicated that they used a home-care provider, with HaH named by one. Both organisations that had home services completely delivered by the hospital reported eligibility levels higher than those using a service delivered through a home-care provider (*Table 10*).

Eligibility for participation in community chemotherapy

In the community setting, patient eligibility criteria focused primarily on suitability of regimens and patient distance from their hospital. Only one organisation expressed eligibility limitations based on which cycle of chemotherapy was being administered; they reported that patients must be fit and have had two cycles in hospital. Two indicated that distance of patient travel was a factor in eligibility, but did not quantify what distances were acceptable. Three quantified the percentage of patients eligible for chemotherapy in the community: one reported that 60% of patients were eligible and 80% of eligible patients accepted; another reported that 10–15% were eligible and 10–15% accepted; and a third reported that 50% of patients were eligible, with 30% accepted (see *Table 10*).

Provision of chemotherapy services at home and in the community

Three organisations delivered chemotherapy in the community using mobile chemotherapy units. The other four organisations that delivered intravenous chemotherapy in a community setting used different locations: two in community hospitals, one in a satellite unit in a primary care centre and another used a room in a local hospice.

There were several similarities between home and community chemotherapy administration. Patients in both settings were cared for between chemotherapy treatments at their regular institutions and given access to standard 24-hour advice telephone lines, and patients were referred to both services by consultants and specialist nurses.

TABLE 10 Patient eligibility requirements for chemotherapy at home or in the community

	Services provided		Private provider delivers some or all aspects of service		Eligibility requirements for home				Eligibility requirements for community				
Organisation identifier	Provides chemotherapy at home	Provides chemotherapy in the community	Home	Community	Number of cycles in hospital	Regimen	Number eligible	Number accept	Number of cycles	Regimen	Distance to hospital	Per cent eligible	Per cent accept
1	✓	✓	–	–	–	–	40	20	–	–	–	60	80
2		✓	–	–	–	–	–	–	2	✓	–	NQ	NQ
3	✓	–	–	–	–	–	–	–	–	–	–	–	–
4	✓	✓	✓	✓	–	–	NQ	NQ	–	–	–	–	–
5	✓	–	✓	–	3	–	< 5	NQ	–	–	–	–	–
6	–	✓	–	–	–	–	–	–	–	✓	✓	10–15	10–15
7	✓	✓	–	–	–	✓	15	50	–	✓	–	50	30
8	✓	–	✓	–	–	–	< 5	70	–	–	–	–	–
9	✓	✓	✓	–	–	✓	–	–	–	✓	✓	–	–
10	–	✓	–	–	–	–	–	–	–	–	–	–	–

–, not applicable, no response; NQ, not quantified.

Organisations that indicated they did not provide chemotherapy at home or in the community

There were 12 organisations that did not provide intravenous chemotherapy at home or in the community; six indicated that they were interested in providing a service and three indicated that they may be interested in providing a service in the future. One organisation had indicated that they provide home chemotherapy, but only provided home trastuzumab. No organisations said that they would not consider providing a community or home service. Of the six organisations that said they would consider providing a service, one organisation was working on a proposal for a service, and another indicated that a service was not offered yet but was at an advanced stage of planning.

Barriers to service delivery

One of the aims of the survey was to identify barriers to service provision in the community and at home from those who provided services, and those who did not provide services. Common concerns existed in both groups. The full set of responses to these questions is available on request. Some commonly perceived barriers highlighted by responders were:

- costs of running a service
- value-added tax (VAT) savings, which were driving which drugs were offered at home rather than the suitability of the drugs for administration at home
- the fact that there might have been less expensive ways to deliver chemotherapy in the community than delivering at home, but current regulations did not allow or incentivise more efficient community delivery
- issues with consultant support for home services
- poor strategic planning
- broad geographical area that would be difficult to serve
- interest in delivering a service but lack of a commissioned service
- limited numbers of eligible chemotherapy regimens
- lack of nursing resources
- lack of suitably trained staff
- a need to convince patients to use the service.

There were several limitations to the survey: the sample was small; the information provided by respondents was generally not very detailed; the survey requested recollections and descriptions from providers rather than service data; and questions were not always interpreted as intended. However, the aim was to provide a picture of current provision and add clarity to the patient pathway, where possible. The survey highlights the wide variation in current provision.

Private provider survey

All nine groups that we contacted responded to the survey but only HaH, Bupa Home Healthcare and Calea Ltd currently provided chemotherapy closer to home. None of the respondents described providing intravenous chemotherapy services in a community setting. However, the survey did not have differentiated questions regarding home and community services, and so a description for a home service did not necessarily preclude the provision of intravenous chemotherapy in a community setting. Both HaH and Bupa ran comprehensive home chemotherapy services that included patient registration; prescription, preparation and delivery of cytotoxic drugs; supply of nurses; patient counselling, and telephone support for adverse reactions; and logistics and waste removal for a variety of chemotherapy regimens (specific regimens were considered commercially sensitive and not disclosed). Calea provided off-the-shelf and compounded methotrexate to NHS trusts in the Yorkshire region inclusive of nurses where necessary. HaH indicated that they provided chemotherapy in the home or community setting to more than 40 NHS trusts. Bupa did not provide information on how many NHS organisations they provided with home or community chemotherapy services.

Further follow-up with the organisations yielded limited results. Questions about customer satisfaction, quality-of-life data, cost data and resource use were generally unanswered. Some providers said that information on these outcomes was commercially sensitive; other organisations might have been non-responsive for similar reasons. HaH responded to some queries, and instructed our team to seek answers related to quality of life, patient satisfaction, adverse events and resource use from their health informatics service, Sciensus Ltd. On investigation it was apparent that information was not freely available from Sciensus. We did not pursue paying for information.

Healthcare at Home provided some useful descriptions of their service via personal communication (S McAndrew HaH, 12 September 2013, personal communication). They indicated that their home chemotherapy service uses a regional hub for northern Europe, with support services for adverse reactions and general patient counselling provided from this facility. They also indicated that next-day service was available to the UK mainland, major islands and northern Europe using their own vehicle fleet from their regional hub. According to HaH, nurse travel to patients and between patients averaged 1 hour. HaH used their own private pharmacy, which might have made them eligible for a zero VAT rating on drugs they delivered in the home, under current UK legislation.[68]

Bupa did not respond to additional requests for information but their website was very informative and included thorough service descriptions and a full list of chemotherapy regimens eligible for home delivery.[69,70] Bupa provided a business example on their website where the cost of a drug administered at home is reduced by 20% compared with NHS administration. This appeared to indicate that private providers were providing drugs with zero VAT liability.[69]

From the private provider survey, it is clear that the consolidated nature of the private providers enabled them to serve larger regions. All private organisations that provided home chemotherapy to the NHS did so across multiple trusts.

Summary of current provision

There was great variety in service provision, with differences in the total number of staff involved, who provided services and how they were provided. The total number of nurses involved in delivering home and community services varied across providers, but the numbers administering each individual treatment were consistent: one at home, and one or two in the community setting.

Private providers were often used for administering home chemotherapy; this usually entailed using a private pharmacy. These private providers appear to have very selective eligibility criteria to their programmes and only accept patients after two or more cycles have been delivered in hospital. The percentage of patients eligible in privately provided programmes was lower than that provided in services that were administered completely by the NHS. Outside private provider requirements for a certain number of cycles in hospital, regimen appeared to be the most important determinant of eligibility, followed by patient performance.

Community settings included three mobile units (chemotherapy bus), two community hospitals, a satellite unit in a primary care centre and a room in a local hospice. Most community providers indicated that the NHS provided all aspects of the service. Regimen and patient fitness for treatment appeared to be the most important determinants of eligibility for home chemotherapy. More patients were eligible for chemotherapy in the community than at home.

Private providers were found to offer a potentially wide variety of regimens[70] and provide comprehensive chemotherapy services to a large number of trusts (HaH), but it was unclear what effect their services had on patient quality of life or patient satisfaction. Private providers were able to take advantage of VAT exemptions for drugs, and provide services across multiple providers, both of which could lead to less expensive and more efficient service capabilities.

Chapter 5 Patient pathway

Overall pathway

Using the evidence identified through the systematic review and survey, and with advice from our advisory group, we have outlined the general pathway that an intravenous chemotherapy patient may follow through the NHS. The pathway involves many steps, some of which are outside the scope of the decision problem this research is addressing. They are outlined, however, to give context to the question that will be addressed.

- Step 1: access and referral to an oncologist.
- Step 2: assessment and decision to treat, patient consent.
- Step 2a: assessment of decision to treat with chemotherapy.

It is anticipated that these three steps (1 to 2a) will be the same regardless of the setting in which the treatment will be delivered. On completion of these three steps a group of patients eligible and willing to receive intravenous chemotherapy have been identified. *Figure 7* depicts the pathway for this population. In addition to the figure, the following is a summary of some of the considerations made at each step in the pathway. The evidence collated from the questionnaires, outlined earlier in *Chapter 4*, suggests that the eligibility criteria for treatment at home may be stricter than the criteria for treatment in the community. Therefore, a proportion of the total population eligible for intravenous chemotherapy will be eligible to receive that treatment in a community setting and a subgroup of those will be eligible to receive their treatment at home.

- Step 2b: assessment of eligibility for treatment at community and/or home.

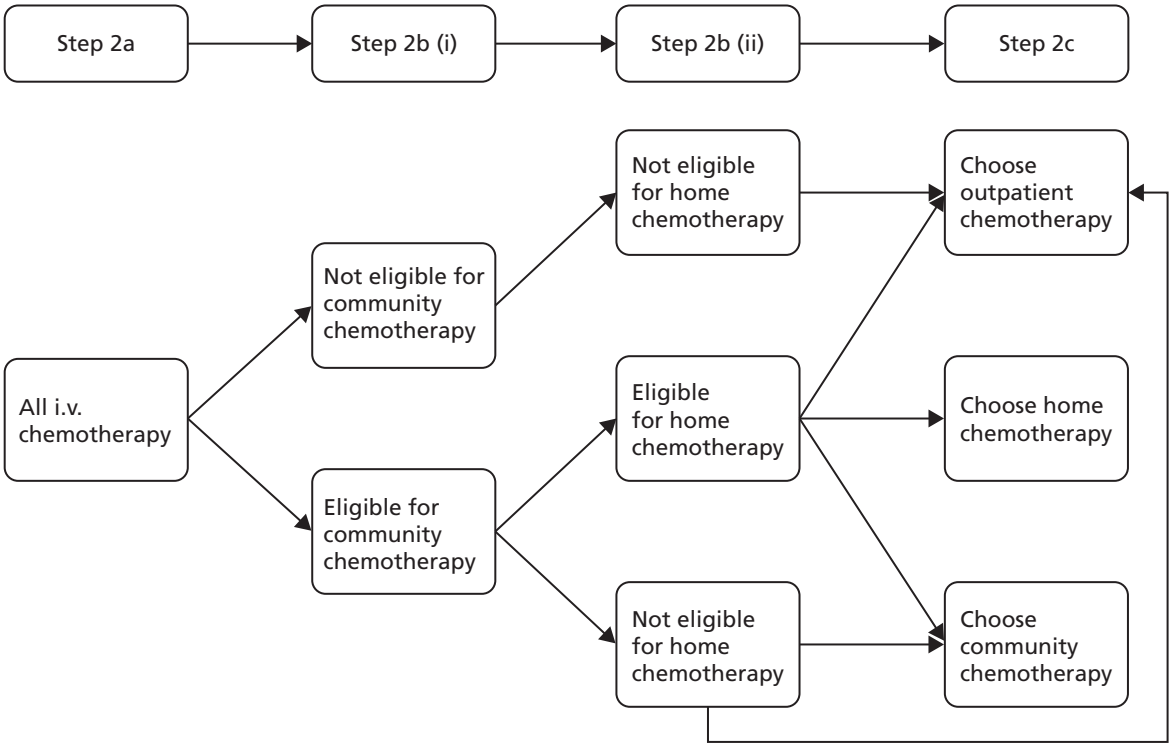

FIGURE 7 Patient pathway. i.v., intravenous.

In any organisation delivering treatments within these settings, individual patient eligibility criteria will be defined [step 2b (i)]. Eligibility criteria are expected to consist of the following elements:

- patient fitness status (ECOG performance status, comorbidities)
- drug regimen suitability (drug stability, length of infusions, low-risk adverse event profiles)
- clinical perception of individual patient probability of being hypersensitive to drugs (this can be mitigated through having one or two cycles in hospital)
- clinical perception of individual patient susceptibility to severe adverse events
- cancer type (breast, lung, colon, etc.)
- cancer stage/grade
- line of treatment (first, second, third)
- neoadjuvant/adjuvant versus primary treatment
- patient age (children, young adults, adults, elderly).

Once patient eligibility is determined, it is expected that an assessment [step 2b (ii)] of the patient's home environment and location would be necessary unless the patient expresses a preference for treatment not to take place at home. The elements considered in any such assessment are likely to include:

- distance from home to hospital or drug preparation unit
- whether the patient lives alone or has support
- whether or not the patient has pets and if they can be removed for the treatment duration
- whether or not the patient has children and if they will be present at treatment delivery
- whether or not the home is of an acceptable cleanliness
- whether or not there is a place for the nurse to wash their hands
- whether or not there is a workspace available.

These assessments may be undertaken by a multidisciplinary team (led by the oncologist and specialist cancer nurse) or by the specialist chemotherapy nurse. These assessments ensure that patients and their homes are suitable. There is also the issue of patient choice. Assuming that the health service organisation is in a position to offer all three treatment settings, there are still a number of considerations for the patients and uptake of treatment in alternative settings is likely to be variable. Across regions, choice and preference may depend on socioeconomic variation, geographical differences and the overall demographics of the regional population.

Other determinants of uptake may be significantly different. It is expected that an individual's choice may be influenced by the following aspects:

- time constraints
- labour force participation
- distance to the hospital
- availability of transport
- cost of transport and parking
- ease of hospital access
- appreciation by some people of a change of location and social interaction
- availability of childcare
- symptom severity
- clinical advice and enthusiasm of health-care workers
- society's acceptance of home chemotherapy
- wish to keep treatment out of the home
- personal aversion/fear of hospitals
- personal relationship with hospital staff
- quality of past hospital care
- provision of safety information
- family agreement and support.

The main focus of this report is on the later part of the pathway, wherein patients eligible for home chemotherapy receive treatment in their chosen location. The decision problem addressed in the economic modelling will not take account of eligibility criteria and how clinical staff might identify people to be offered home intravenous chemotherapy as a treatment option. Instead, it commences with an eligible population and addresses the question of which setting is most cost-effective for this population.

Decision model

One of the aims of the systematic review was to identify relevant data for a decision model. The systematic review produced little relevant evidence to facilitate answering the decision problem robustly. In an attempt to illuminate the issues surrounding the cost-effectiveness of delivering community-based chemotherapy, we have taken the best available evidence identified during the review and used this to undertake exploratory decision modelling.

The systematic review identified nine economic evaluations that compared chemotherapy in an outpatient hospital setting with chemotherapy administered in a home and/or community setting. The limitations of these economic evaluations are described in *Chapter 3* (see *Cost-effectiveness studies*). This report is targeted for a UK audience and so the most relevant economic evaluations for model inputs were the OUTREACH trial[4] and Pace *et al.*[29] Both of these studies were set in the UK and provided some, albeit limited, information on costs and outcomes for a relevant UK population.

The systematic review identified eight studies which were not full economic evaluations but reported costs and/or resource use. Six studies were not from the UK; two only provided cost information[42,48] and the remaining four were not included for reasons of generalisability.[27,28,35,37] The two UK studies were not sufficiently detailed to provide any additional information above that presented in the OUTREACH trial.[30,71]

In the UK, cost–utility analyses (CUAs) are generally considered the most relevant type of economic evaluation to help to inform decision-making.[72] Cost–utility studies represent intervention costs and intervention benefits measured in QALYs. QALYs measure a person's remaining quantity and also quality of life. These analyses usually produce ICERs, calculated as the costs of intervention A minus the costs of intervention B, divided by the benefits of intervention A minus the benefits of intervention B. These analyses can contain multiple interventions, in which case each intervention is compared with the next least costly intervention. Because the OUTREACH trial produced a CUA in line with UK methodological guidelines, the base-case model replicates data from the OUTREACH trial with some augmentations made where necessary. The following sections outline the model structure, parameters and results.

Model structure

A simple decision model was developed in Excel (Microsoft Excel 2010, Microsoft Corporation, Redmond, WA, USA) to assess the cost-effectiveness of intravenous chemotherapy delivered in the home, community or outpatient setting in a population considered eligible for home treatment. *Figure 8* shows this patient pathway and how it relates to the broader issues around the implementation of chemotherapy at home or in the community. Many aspects of the implementation of community and home chemotherapy are not part of the decision problem addressed by the model and these are shaded green.

All of the patients in the model are assumed to be eligible for home chemotherapy. They then choose where they receive their treatment, and incur costs and accumulate QALYs over the time horizon of the decision-tree model.

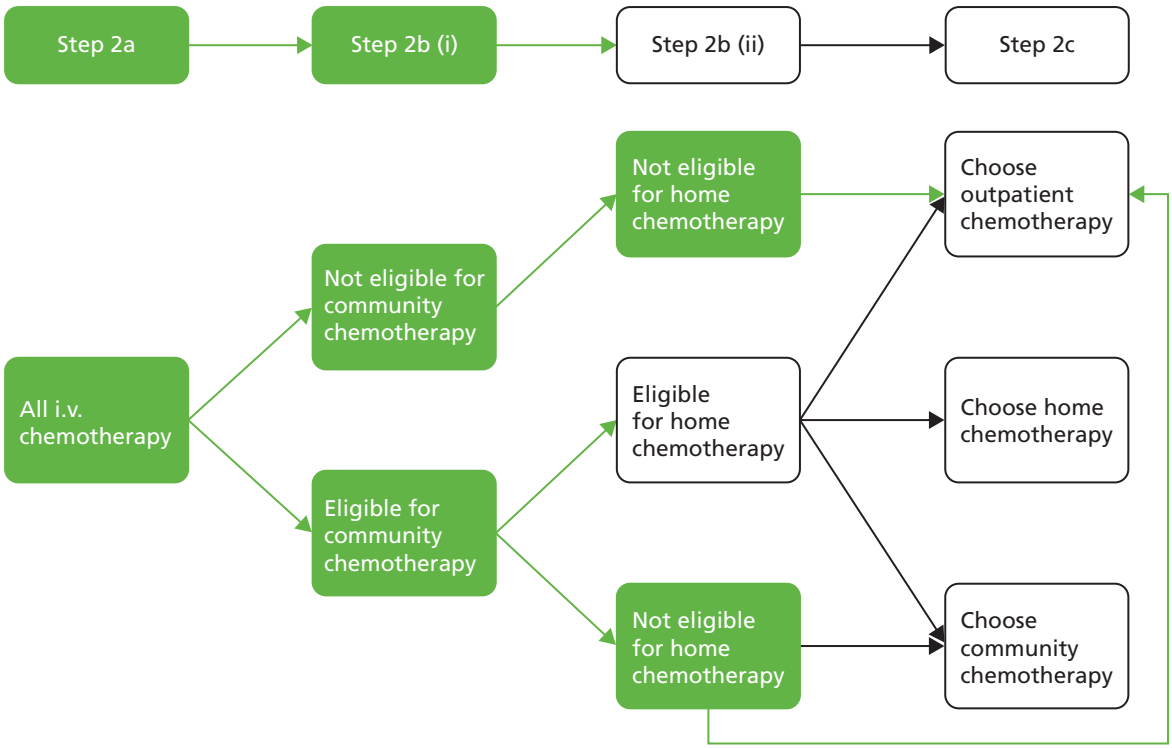

FIGURE 8 Modelling patient pathway. i.v., intravenous.

The patient population of the model is assumed to replicate patient characteristics from the OUTREACH trial: patients were above the age of 18 years with an ECOG performance status of 0–2, lived within a 30-minute drive of the recruiting hospital, and either were about to commence or had commenced a course of cancer treatment with standard infusions lasting < 4 hours for a minimum of 12 weeks with intent to treat, cure or provide palliative care. Patients were required to have a life expectancy > 6 months and be capable of independent transportation to the hospital. Patients were not taking any unlicensed drug as part of their treatment. Patients randomised between the three settings were broadly similar in ECOG performance, treatment intent and gender. There were small differences in cancer types in each arm.

We ran the model for a cohort of cancer patients receiving intravenous chemotherapy. The distribution of patients across the model arms was derived from anticipated patient choices based on data from the OUTREACH trial. Cost and utility weights are applied dependent on the treatment setting. Owing to limitations with the trial data, we elected not to extend the time horizon of the model beyond that of the trial (12 weeks) to avoid introducing more uncertainty through the use of extrapolation. The time horizon was 12 weeks and, as a consequence, the cost and utilities were not discounted in the base case. Costs are reported in 2012 pounds sterling.

Model parameters

Patient choice

The initial distribution of patients to different settings within the model was determined by patient choice assumptions derived from OUTREACH.[4] As highlighted in the systematic review of clinical effectiveness, patients may participate in a trial because they want the new treatment; others may elect not to participate to ensure that they are not exposed to unwanted treatment. In OUTREACH, patients who wanted outpatient hospital chemotherapy or did not want to receive treatment in a particular setting could simply opt not to participate in the trial. The proportion of patients in the model choosing each setting was, therefore, adjusted for recruitment bias, based on methodology from King *et al.*[31]

Although OUTREACH reported preference data, it did not utilise a crossover design and patients were asked whether or not they would prefer to continue treatment in their allocated setting. These patients experienced only one setting during the trial and so it is unclear if their decision was informed by past experience of chemotherapy in the hospital outpatient setting or if patients were naive to chemotherapy. Owing to this, it was unclear in which setting any given patient would choose to have treatment had they experienced multiple settings.

To adjust for this limitation of the OUTREACH data we assumed that the patient population had had weak preferences as in King *et al.*[31] Assuming indifference to treatment settings may be considered conservative as we cannot know the motivation of patients who chose to participate in the trial; they might have participated because of preference for treatment settings other than the outpatient default. Patients who chose not to participate in the trial owing to a stated preference were by definition not indifferent to the setting and so we needed to adjust for this potential bias. Our adjustments took into account patients' expressed reasons for preferring one setting over another as described in *Chapter 3* (see *Qualitative studies*) and the analysis in King *et al.*,[31] where patients who had declined to participate in the trial due to strong preferences were reintegrated into the data to adjust preferences; this resulted in 48% of patients preferring chemotherapy at home, as outlined earlier (see *Chapter 3*, *Clinical effectiveness studies* and *Satisfaction and preferences*).[31,54]

In OUTREACH, 33 patients were randomised to home, 32 were randomised to community (GP practice) and 32 were randomised to outpatient. Fifty-three patients declined to take part in the trial: 35 wanted an outpatient setting; 16 did not want chemotherapy in a GP practice; and two preferred chemotherapy at home. Following the King *et al.*[31] methodology, these 53 patients excluded owing to preference were added to those who chose to participate in the OUTREACH trial with the assumption that patients with a stated preference for outpatient would receive outpatient and those with a preference against the GP or home setting would be split evenly between the alternative settings. As the results from the King *et al.*[31] study suggested that overall patient preference may not be particularly strong, we assumed patients who stated no preference to be indifferent to treatment setting allocation.

After adjustments, the resultant probabilities suggested that 27.3% of patients would choose to have their chemotherapy at home, 22.0% would choose to have it in the community and 50.7% would choose the hospital outpatient setting. In a probabilistic sensitivity analysis, a Dirichlet distribution was used to reflect the uncertainty surrounding choice. *Table 11* shows the transition probabilities between states used within the model and the mortality rate applied to all states.

At this point, including patient choice does not affect OUTREACH results because any benefits and costs in a setting are divided by the number of people in that setting and so they are cancelled out. However, if throughput is introduced to the model, and this throughput determines fixed costs and potential savings due to economic efficiency, then patient choice will impact the results of the model.

TABLE 11 Transition probabilities for the decision model

Intervention	Mean	*n*	SE	Distribution	Source
Patients choose home	0.273	43		Dirichlet	OUTREACH,[4] King *et al.*[31]
Patients choose community	0.22	33		Dirichlet	OUTREACH,[4] King *et al.*[31]
Patients choose outpatient	0.507	76		Dirichlet	OUTREACH,[4] King *et al.*[31]
Probability of death	0.06	1,278,602	0.0018	Beta	ONS Cancer Survival in England 2012[73]

ONS, Office for National Statistics; SE, standard error.

The model allows for the possibility that patients may die based on Office for National Statistics mortality statistics for 20 common cancers.[73] Although there were no mortalities recorded in the OUTREACH trial, it is possible that, in practice, some patients receiving chemotherapy will die over a 12-week or longer period. The mortality rate was assumed to be the same for each setting and so had no effect on the model outcomes. The mortality parameter was included to allow for longer model lengths and to improve the face validity of the model.

Patient quality of life

The OUTREACH trial reported the number of QALYs gained over the 12-week length of the trial. Utility values were derived using the EQ-5D questionnaire as completed by the patients in the trial. Questionnaires were completed at baseline and 4, 8 and 12 weeks; only outcomes at 12 weeks were analysed. The model uses the 12-week QALYs derived from OUTREACH. These data are treated as utility scores, assuming constant utility over the time period, implying that any QALY gains are equivalent to multiplying the utility score at 12 weeks by 12/52. The QALYs in OUTREACH were reported without baseline values and so the base-case model has no adjustment for baseline values. *Table 12* presents the utility values in the model derived from OUTREACH. The uncertainty in the underlying utility data was represented using beta distributions in probabilistic sensitivity analysis. The utility value for the death state was assumed to be the customary value of zero.

Costs

The original OUTREACH publication reported total costs with no details of what these comprised. We obtained additional cost category data from the authors.

Total costs were divided into the following categories: inpatient, outpatient, day hospital, A&E visits, community care, medication (excluding cancer drugs) and nurse contact. Follow-up data provided by the authors were reported as average costs per patient for each category in each setting, with no reported resource use. However, included data suggested that A&E visits, as a cost category, cost on average £3–4 per patient. Clarification was sought from the authors whether the value they reported was the average number of visits, as their table appeared to indicate, or the total number of visits to A&E for each treatment arm, but no additional information was provided. Therefore, we have assumed that this is an error and that the number represented total visits to A&E per arm, rather than the average costs of those visits. In order to produce the average cost of each emergency room visit, we multiplied the NHS reference cost for A&E visits by the number supplied from the OUTREACH trial and divided this by the number of participants in each arm. The cost of one A&E visit without any follow-up visits according to NHS reference costs was £122 in 2011–12.[74]

Cost data provided on request from the OUTREACH trial did not contain SDs or standard errors; aggregate costs reported in the published study provided SDs for total costs in each study arm. We assumed that the proportion of the SD to the mean for cost categories would be similar to the proportion of the SD to the mean for total costs. The proportions of the SD of costs to mean costs are shown in *Table 13*. We assumed that the proportion of the SD to costs for all arms would be the average of the three, that is 75%.

In a probabilistic sensitivity analysis, gamma distributions were used to represent costs, as the skew of the gamma distribution and bounding between zero and positive infinity make it a good choice for representing costs. *Table 14* incorporates all updated costs from the OUTREACH trial inclusive of our

TABLE 12 Utility values used in the decision model

Intervention	Mean EQ-5D	*n*	SD
Outpatient	0.754	14	0.147
Home	0.715	15	0.230
Community (GP practice)	0.828	19	0.173

TABLE 13 Proportion of SD to mean cost from OUTREACH trial

Setting	SD (£)	Mean cost (£)	Proportion of SD to mean cost
Hospital outpatient	1831	2221	0.82
Community (GP practice)	1759	2497	0.70
Home	1590	2139	0.74

TABLE 14 All costs used in the decision model

Intervention	Mean (£)	*n*	SD (£)
A&E visit costs	122.00	150,041	41.30
Outpatient			
Inpatient	321.12	13	240.84
Outpatient	880.74	13	660.56
Day hospital	716.57	13	537.43
A&E visits	37.54	13	28.15
Community care	210.64	13	157.98
Medication (non-cancer)	8.26	13	6.20
Nurse diaries	151.78	13	113.84
Total costs: outpatient	2326.65	13	1744.99
Home			
Inpatient	215.80	20	161.85
Outpatient	588.54	20	441.40
Day hospital	292.20	20	219.15
A&E visits	18.30	20	13.73
Community care	242.64	20	181.98
Medication (non-cancer)	11.36	20	8.52
Nurse diaries	857.00	20	642.75
Total costs: home	2225.84	20	1669.38
Community (GP)			
Inpatient	367.58	17	275.68
Outpatient	617.45	17	463.09
Day hospital	214.77	17	161.07
A&E visits	21.53	17	16.15
Community care	284.98	17	213.73
Medication (non-cancer)	16.52	17	12.39
Nurse diaries	1073.83	17	805.37
Total cost: community	2596.65	17	1947.49

assumptions modifying A&E costs and inflating prices using 2011–12 Personal and Social Services Research Unit price indices for medical services.[75] The cost of an A&E visit was derived from 2011–12 NHS reference costs;[74] all other costs were derived from the OUTREACH trial.[4]

Cost-effectiveness results

The base-case deterministic model results are presented in *Table 15*. These results do not account for uncertainty; in order to do this, a probabilistic sensitivity analysis was undertaken varying all model parameters within their assigned distribution for 10,000 simulations. The results of the probabilistic analysis are presented in *Table 16* and in graphical form in *Figures 9* and *10*.

In the base case, home chemotherapy is both the least costly and the least effective treatment setting, followed by outpatient chemotherapy, which has an ICER of £11,201 per QALY compared with the home setting. Assuming the standard National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold willingness-to-pay range of £20,000–30,000 per QALY gained, the ICER of £15,882 per QALY for community chemotherapy compared with outpatient chemotherapy indicates that delivering chemotherapy in a community setting is cost-effective.[72]

Table 16 shows the probability of cost-effectiveness of the different settings at several values. NICE guidance also advises that ICERs greater than £30,000 per QALY may be considered for treatments that meet criteria for end-of-life care,[72,76] which may be important for specific chemotherapy regimens that meet end-of-life care criteria.

Table 16 and *Figures 9* and *10* clearly demonstrate the high level of uncertainty surrounding any decision based on the OUTREACH trial data. There are no treatments that have a high probability (> 60%) of being the most cost-effective treatment setting between a £0 and £30,000 per QALY willingness-to-pay threshold. Only at a threshold of £50,000 per QALY does the likelihood of community chemotherapy being the most cost-effective option rise above 60%. Home and outpatient chemotherapy never have a probability of being the most cost-effective treatment of much more than 45%, and this only occurs at a willingness to pay of £0 per QALY with the treatment setting being home chemotherapy. *Figure 10* shows that up to a threshold ICER of £7200 per QALY chemotherapy delivered in the home setting is the preferred option, up to an ICER of £16,400 per QALY outpatient chemotherapy is the preferred setting, and above this value community chemotherapy is preferred.

TABLE 15 Base-case cost-effectiveness results

Intervention	Costs (£)	QALY	Incremental costs (£)	Incremental QALY	ICER (£)
Home	2225.84	0.165	–	–	–
Outpatient	2326.65	0.174	100.81	0.009	11,200.89
Community	2596.65	0.191	270.00	0.017	15,882.39

TABLE 16 Probability of cost-effectiveness at various thresholds

	Threshold values (£/QALY)				
Setting	£0	£10,000	£20,000	£30,000	£50,000
Home	0.462	0.351	0.260	0.196	0.128
Outpatient	0.383	0.376	0.340	0.300	0.218
Community	0.155	0.273	0.400	0.504	0.655

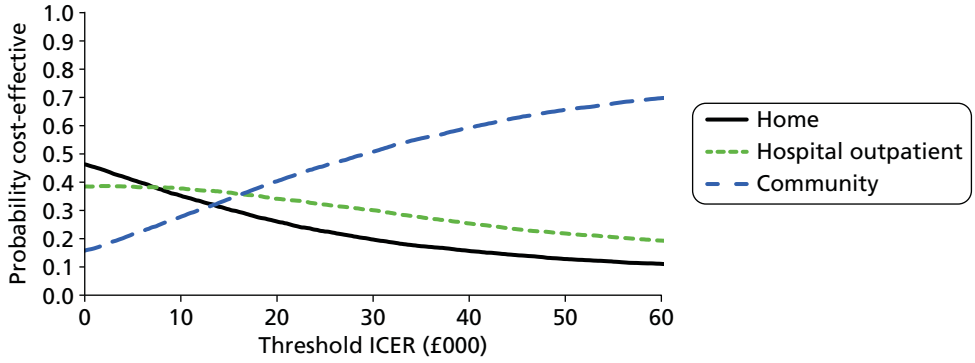

FIGURE 9 Cost-effectiveness acceptability curves.

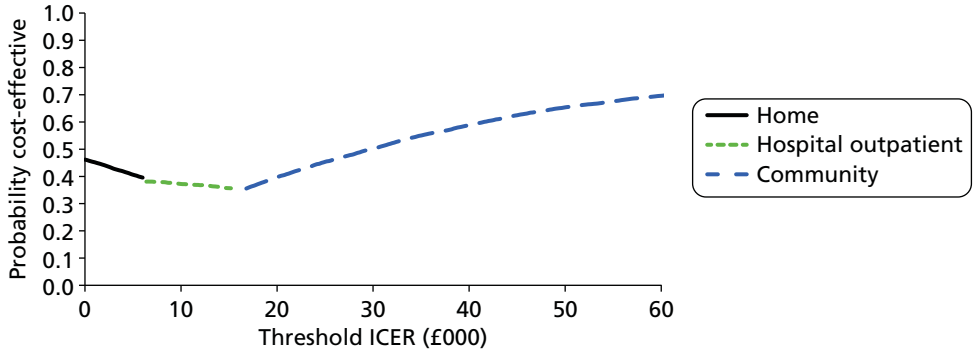

FIGURE 10 Cost-effectiveness acceptability frontier.

While this model based on the OUTREACH trial found that the most cost-effective option across accepted willingness-to-pay thresholds in the UK was chemotherapy delivered in the community, as previously stated its purpose is exploratory and the results should not be considered robust or used to inform decisions. Model limitations include:

- The OUTREACH trial had very small numbers of patients returning health economic outcomes for the CUA (no more than 20 for cost outcomes, and no more than 19 for QALYs).
- No differences in health-related quality of life were statistically significant.
- The precise details of each of the settings used in OUTREACH may be different from those used in the same setting in a different location.
- The model is simplistic and may not represent important nuances in delivering chemotherapy.
- The generalisability of the patient population is unclear.

Sensitivity analyses

We used sensitivity analyses to further explore impacts of assumptions and small adjustments on data. The limitations of the model meant that an exhaustive suite of sensitivity analyses might not be helpful and could possibly mislead readers. For this reason we performed only three formal sensitivity analyses:

- Scenario 1: utilities adjusted for baseline.
- Scenario 2: the mean cost of community care in the home setting was made equal to the mean cost of community care in the community (GP) setting (£285) and the mean nurse diary costs for the community (GP) setting were made equal to those in the home setting (£857).
- Scenario 3: mean inpatient stay costs in the home setting were made equal to community (GP) setting costs (£368).

These analyses highlight the uncertainty in the outcomes and the impact on the cost-effectiveness of each setting as a result of making small plausible changes to the data. The results of all sensitivity analyses are reported in *Table 17*. In addition to these analyses, the potential implications of using different analytical perspectives are discussed, as well as potential effects of VAT exemptions on provision of chemotherapy services in the home.

Adjusting for baseline imbalances in utility scores

Information provided from the OUTREACH trial indicated that the authors had adjusted QALY gains for baseline imbalances. Because no baseline values were reported and only a difference in difference analysis was provided, this sensitivity analysis assumes that the difference in baseline values is maintained in the difference in final QALYs gained. To maintain consistency, these values were converted to utility scores for use in the model. *Table 18* shows the utility adjustments made in the OUTREACH data.

Using these adjusted values in the model changes the ICER of the chemotherapy settings. In the base case, chemotherapy administered in a community setting was the most effective option at a threshold of £20,000. In this sensitivity analysis, chemotherapy in the community is both more costly and less effective than administration in the outpatient setting. The ICER for outpatient chemotherapy compared with chemotherapy in the home setting also improves.

TABLE 17 Results of scenario analyses

Intervention setting	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Scenario 1					
Home	2225.84	0.164	–	–	–
Outpatient	2326.65	0.174	100.81	0.010	10,080.80
Community	2596.65	0.165	270.00	–0.009	Dominated
Scenario 2					
Home	2268.17	0.165	–	–	–
Outpatient	2326.65	0.174	58.47	0.009	Dominated
Community	2379.82	0.191	111.64	0.026	4294.03
Scenario 3					
Outpatient	2326.65	0.174	–	–	–
Home	2377.62	0.165	50.97	–0.009	Dominated
Community	2596.65	0.191	270	0.017	15,882.39

TABLE 18 Utility adjustments for scenario 1

Intervention	Base-case QALYs	Base-case utility score	Adjusted QALYs	Adjusted utility score
Home	0.165	0.754	0.164	0.711
Outpatient	0.174	0.715	0.174	0.754
Community	0.191	0.828	0.165	0.715

This analysis emphasises the uncertainty surrounding the utility values used in the model. Given the small sample size in the OUTREACH trial and the suggestion of baseline differences, the utility data cannot be considered reliable. It is likely that the quality of life of patients depends on their disease, treatment status (palliative, supportive or curative), age, and other factors that the OUTREACH data may not have captured. Clarification was sought from the authors on whether or not the data were adjusted for patient characteristics other than baseline EQ-5D scores, but none was received. Given the small patient numbers, it is unlikely that any such adjustment would have been plausible or would reduce the uncertainty. Further research is necessary to confirm or refute differences in patient quality of life between settings.

In scenario 2, making the mean cost of community care in the home setting equal to the mean cost of community care in the community (GP) setting, and the mean nurse diary costs for the community (GP) setting equal to those in the home setting, resulted in outpatient care being extendedly dominated; this means that a hypothetical combination of home and community chemotherapy services would be more cost-effective than outpatient chemotherapy on its own. In scenario 2, chemotherapy in the community setting is the most cost-effective option with an ICER that is lower than the base-case analysis. Similarly, scenario 3 makes home more costly than outpatient and it remains less effective. In scenario 3, home is dominated and community is the most cost-effective option.

Other areas of interest for exploration

The perspective of all our modelling analyses is the NHS and Personal and Social Services perspective (only costs to the NHS and Personal and Social Services are included). Other perspectives could be analysed and may produce different results.

Some economic evaluations included in our systematic review included patient or carer costs: patient travel costs;[29] parent travel costs, payments for physician/care provider visits, medication, babysitting, lost productivity and government transfer payments;[33] and patient travel costs.[34] These are valid perspectives, but their relevance to NHS decision-makers may be limited even though they are interesting.

The Centre for Health Economics, University of York, published a contingent valuation study of patient time.[77] This study asked patients to value different usages of their time such as time to start of treatment (between scheduling an appointment and receiving treatment), travel time, time waiting at a health facility for treatment and time receiving treatment.

In our model, time to start of treatment and time receiving treatment are expected to be independent of the setting and so only values related to travel time and waiting time are reported. The Centre for Health Economics study measured Dutch patients' valuations of travel and waiting time for patients in three treatment areas (radiotherapy, orthopaedics and rehabilitation) and found that they valued each hour of travel time at £11.54 and each hour of waiting time at £34.76.[77] Chemotherapy patients were keenly aware of how time spent travelling to hospital and waiting for treatment had negative impacts on their time and energy. Including valuations of patient time could have significant impacts on the cost-effectiveness of treatment settings for chemotherapy. However, our systematic review identified only limited information on time spent travelling to and waiting in hospitals in the UK.

Several respondents in our survey of provision mentioned that drugs delivered at home were exempt from VAT (current rate 20%) and that these savings were used to finance home chemotherapy services. This view was reflected by the advisory group. Private providers have used VAT savings in trying to market their home services to NHS providers.[69] HM Revenue & Customs has indicated that medicines delivered in the home may be eligible for a zero rating for VAT where requirements are met regarding drug use and provision.[68]

Considering that cost differences between the settings were small, reducing drug costs by 20% could alter cost-effectiveness decisions on home provision of specific chemotherapeutic drugs. Drug costs were not included in our model as they were not included in the OUTREACH data. However, it is likely that drug costs make up a significant proportion of the total cost of treatment. This will be particularly true in the case of newer chemotherapy drugs where the cost of the drug may represent most of the total treatment cost. In these instances the impact of VAT exemptions may have an impact on where these drugs are prepared and delivered.

Some of the issues outlined will not be relevant across the whole NHS, but local service configurations may make them worthy of further investigation should data become available.

Chapter 6 Discussion

The aim of this project was to investigate the impact of the delivery of intravenous chemotherapy in different settings on quality of life, safety, patient satisfaction and costs.

We performed three systematic reviews to provide a complete overview of the available published evidence base. We supplemented the published evidence with a survey of current practice to better understand the variation in chemotherapy deliver practices in the UK and facilitate the structuring of an economic decision model. In this section we present a summary of those findings and their strengths and limitations and bring together the elements of this mixed-methods project to draw summary conclusions and highlight the implications for practice and further research.

Key findings

The results of this study highlight avoidable study design and reporting limitations, and inherent and sometimes unavoidable difficulties, which arise when conducting primary studies to compare chemotherapy settings. Although several studies were appropriately designed to minimise avoidable biases, conducting randomised trials of chemotherapy settings nevertheless appears difficult in terms of both patient accrual and recruiting a population to enable an unbiased evaluation of the settings. Consequently, few robust conclusions can be made about the clinical effectiveness and cost-effectiveness of the different settings. However, a prevalence of qualitative data enabled a broad evaluation of patient, relative and caregiver experiences, with additional input from health-care professionals.

We identified eligible randomised trials and economic evaluations but there was a lack of useful data to inform and populate a decision model, and little evidence of clinically relevant differences between settings in terms of quality of life, and clinical and psychological outcomes (even though the biases when recruiting patients would have been expected to favour the home or community settings). The synthesis of qualitative studies indicated that decisions and preferences about intravenous chemotherapy treatment setting are strongly influenced by a desire to maintain normality. The modelling developed in our study was necessarily exploratory in nature owing to the limitations of the existing evidence base.

There was little evidence to indicate any effects of setting on quality of life. Trial samples sizes were likely too small to detect any such effects. It was unclear whether or not the quality-of-life assessment tools used were sensitive enough to detect differences between settings. The only potentially meaningful differences evident from the clinical effectiveness review were for some patient satisfaction and preference outcomes. However, strength of preference was studied in only one trial and preferences appeared not to be strong in around one-third of the patients who said that they preferred home chemotherapy. These results indicated that time was more important than setting for those patients.[31] There were no comparative studies of how preferences might change with other factors (such as distance from hospital, financial costs, outpatient environment and nurse–patient relationship). The limited adverse event evidence available gave no indication that there need be any safety concerns when delivering intravenous chemotherapy in either the home or the community setting.

The qualitative studies provided evidence from health professionals, patients (adults and children), parents, carers, siblings and partners. The data focused on experiences of outpatient and home settings for intravenous chemotherapy and included some data on community settings including mobile bus units. The range of participants and experiences suggests that these data provide relatively comprehensive coverage.

We have presented a line of argument around barriers and perceived costs associated with non-outpatient settings. Barriers to service provision centred on costs/resources, lack of support from key referring staff and the need for more training or additional nurses. Staff expressed concerns about their personal safety in relation to home chemotherapy services.

These issues were mirrored in the survey data presented in *Chapter 4* and summarised in *Table 19*. The second line of argument focused on factors influencing patient satisfaction with intravenous chemotherapy across locations. Elements such as communication, information, privacy, rapport and individuality of treatment are unlikely to be unique to chemotherapy treatments, but they indicate key areas where small changes could result in substantially improved satisfaction.

The key line of argument derived from the qualitative data states that decisions and preferences about intravenous chemotherapy setting are rooted in attempts to maintain normality. Various factors push patients towards preferring hospital outpatient settings (mostly safety and expertise) while others pull patients towards other settings (in order to have some control over resources, such as time or energy). Medical expertise was the largest component which favoured outpatient treatment; however, this was seen as a trade-off against other settings which facilitated more normality in everyday life. Time was one of the largest factors that drew patient preference away from outpatient settings; it is important to understand that this is about more than waiting times, travel time and length of appointment. Cancer patients and their families were very conscious of the limited resources at their disposal in terms of time and energy. When chemotherapy treatment absorbed too much of these resources, the resulting fatigue impacted heavily on every other aspect of their life. This suggests that complaints about waiting time should be seen in a broader context.

TABLE 19 Barriers to provision

Qualitative synthesis	Survey data
Staff personal safety concerns	
Reluctance to treat in other locations	Lack of consultant support for the service
	Difficulty convincing patients
Adverse event concerns	Limited eligible treatment regimes
Lack of professional support	Regulations interfere with cost-effective provision
Capacity concerns	Practical difficulties
	Lack of nursing staff
Cost of the service (patient and staff views)	Concerns about costs
Lack of communication between health professionals	

Limitations of the evidence and of the review

Clinical studies: recruiting a representative and unbiased population

A key issue to consider when interpreting the results of the randomised trials included in this review is their generalisability. Although many studies (but not all) invited all eligible patients to participate, the nature of the interventions in question (the settings) meant that potential participants were likely to have pre-trial perceptions (opinions and likely preferences) about the interventions they might receive. This is an uncommon problem during randomised trial recruitment because patients typically have limited information on which to base prior perceptions (for at least one of the interventions being studied). In most intervention trials it would be difficult for invited patients to attempt to compare the likely benefits and harms of the interventions for them as individuals. Exceptions would include trials evaluating chemotherapy settings, some behavioural intervention trials,[78] and trials of participative interventions (such as self-monitoring, rehabilitation and counselling interventions).[79]

It is unsurprising that many of the patients who declined to participate in the trials in this review did so because they wanted to receive their chemotherapy in a hospital outpatient setting (or did not want the home setting). By declining to participate, patients would guarantee that they receive chemotherapy in their preferred setting. Conversely, patients who wanted to receive chemotherapy in the home (or community) setting may be likely to accept their invitation to participate in a trial if it were the only route by which they may receive chemotherapy at home or the only way of avoiding the hospital outpatient setting. Consequently, the trial populations in this review are likely to over-represent hospital-averse (or home-inclined) patients, and under-represent patients who are keen to receive chemotherapy in a hospital environment. It is important that the results of these trials are interpreted with this in mind; the trial populations are likely to prefer, to be more satisfied with, and to have a better quality of life, with home or community chemotherapy than with hospital outpatient chemotherapy. Only one trial considered the implications of this issue by performing additional analyses.[31]

Problems are also often encountered in recruiting sufficient numbers of patients into oncology trials, although the reasons for limited accrual are not always easy to identify. A study of 82 oncology trials found that therapeutic trials achieved sufficient accrual more often than non-therapeutic trials, but that shorter consent forms, fewer exclusion criteria and simplicity of trial design were not associated with achieving sufficient accrual.[80] Many of the 82 trials were stopped early because of insufficient accrual. The authors noted a need for research to better inform patient accrual prediction practices (a trend towards accrual sufficiency was observed for trial protocols containing documentation supporting predicted accrual goals). All the trials in our review randomised fewer than 100 participants and almost all had slow rates of recruitment.

A systematic review which assessed studies of patients' attitudes and barriers to participation in cancer trials found that barriers to participation were protocol-related, patient-related or physician-related. The most common reasons given as barriers included concerns with the trial setting; a dislike of randomisation; general discomfort with the research process; complexity and stringency of the protocol; presence of a placebo or no-treatment group; potential side effects; being unaware of trial opportunities; the idea that clinical trials are not appropriate for serious diseases; fear that trial involvement would have a negative effect on the relationship with their physician; and their physician's attitudes towards the trial.[81]

Cost-effectiveness studies, exploratory economic modelling and brief survey

Studies in the cost-effectiveness review were generally poor quality; most were from outside the UK and most did not report resource use or unit costs, and so their generalisability to the UK was limited. Given these limitations, the evidence identified was of limited usefulness for informing a de novo economic model. Sample sizes were generally small and studies were subject to broad uncertainty.

Data from the OUTREACH trial were used to structure and populate a model to enable exploration of cost-effectiveness. However, these data were derived from a small number of trial participants; no more than 20 and as few as 13 patients contributed cost or QALY data for any trial arm. We addressed some of the data limitations using assumptions; where possible these were validated with the authors, but this was not possible in all instances.

The three settings used in OUTREACH may not be representative of all available settings. There appears to be large variation in how UK services are delivered and it remains unclear that the three options modelled would be viable for all organisations. Many will not be in a position to offer more than one alternative to outpatient setting. Owing to capacity constraints, geographical location or other organisational structures, the alternative(s) offered may not constitute a choice. It is possible that some patients may not have multiple options for how they receive their treatment and may not be given a choice that includes settings. Further, it was clear from the survey that third-party providers and chemotherapy buses are already providing treatment closer to home and in the home, but owing to data limitations we were not in a position to include these options as comparators in the model.

The brief survey of NHS and private providers was not intended to be comprehensive and so provided only limited information. The number of responses was relatively low and might not have been representative of the entire NHS, but nevertheless provided a rapid overview of the variation evident in current practice.

Qualitative studies

All of the studies evaluated a new or proposed service against an existing, perhaps struggling, hospital outpatient setting. As discussed previously, participants were drawn from a biased sample. Methodologically, the most common weakness was lack of reflexivity and consideration of the authors' impact on the data, which reduces the reliability of the findings.

In the review it would have been ideal for us to involve another member of the review team in the synthesis process (rather than an external colleague) but this was not possible owing to limited experience of qualitative data. Our use of online web-based translation services for one paper rather than an experienced translator might have resulted in some loss of meaning or mistranslation.

Strengths of the review

This is the first systematic review to compare the effects of home, community and hospital outpatient settings. The only other systematic review in this area compared only the home and hospital outpatient settings and was broader in terms of the eligible populations (studies of patients taking oral chemotherapy or other intravenous cancer therapies were included).[82] This 2010 review concluded that there was no current evidence that home therapy has any beneficial effect on quality of life or response to chemotherapy, although the trials were not powered to detect these outcomes.

Our review was performed according to CRD guidance and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Our comprehensive searches to identify studies located several unpublished studies. A further strength is that we included non-randomised and single-setting studies.

The qualitative review followed an established method (meta-ethnography), using qualitative data analysis software (NVivo) to clearly track which studies contributed to each code; there was oversight from a second reviewer with qualitative expertise and there was discussion of code and line of argument development. Quality assessment was carried out based on clearly defined criteria that are linked to the reliability of the findings rather than fidelity to a particular method.

Our cost-effectiveness review represented a wide variety of potentially relevant outcomes including NICE's preferred measurement of health-related quality of life (EQ-5D) and cost and resource use data from the UK. The model has limitations, but was based on UK data from a trial that compared three different settings. The trial used QALYs and UK costs from the NHS perspective, both of which are in line with NICE methodological guidance. By presenting the modelling we aimed to highlight the uncertainty in the data and the impact of different assumptions when undertaking decision modelling in areas of such variability in service delivery and data uncertainty.

Patient and public involvement

To ensure patient and public involvement (PPI) we recruited two representatives to the advisory group for this project. One representative had received chemotherapy treatment for cancer and the other has a wealth of experience in PPI. They were involved from the proposal stage helping to shape discussions around choice of outcome measures and inform the researchers on issues of importance to patients. As active members of the advisory group, both representatives were invited to review drafts and to comment on the full report before submission. Comments from the PPI representatives indicated that they found the process interesting but felt unable to contribute in detail as the focus was on discussing existing research rather than directly shaping the treatment itself.

Patient and public involvement within the framework of a systematic review is often less about directly influencing the methodology itself, but rather can help to sensitise the researchers to the outcomes of importance to patients. Within this project, PPI helped to emphasise the importance of patient choice and preference rather than just concentrating on clinical outcomes. Such outcomes are more likely to be reported in mixed-methods or qualitative studies, and so it was important to ensure that our searches and inclusion criteria were able to capture such studies.

Chapter 7 Conclusions

Few robust conclusions can be made about the clinical effectiveness and cost-effectiveness of the different settings in which intravenous chemotherapy is administered. This is largely a consequence of the difficulties encountered during the clinical trials. There was a lack of useful data to inform and populate an economic decision model, and little evidence of clinically relevant differences between settings in terms of quality of life, and clinical and psychological outcomes. The results from qualitative studies indicated that decisions and preferences about treatment setting are strongly influenced by a desire to maintain normality.

Implications for research

Study design

Recruitment bias and patient accrual problems are likely to be difficult to overcome in randomised trials that use conventional study designs. A more useful and representative study design might be to nest a RCT within a larger observational cohort of patients; ambivalent patients could be randomised and patients with preferences could receive their preferred setting. Such a study might also make use of the qualitative data themes identified in our review, and incorporate them into questionnaires for use before any chemotherapy is initiated and after chemotherapy in a particular setting is completed. Efficacy estimates would result from the randomised component of the study and any additional influence of motivational factors could be studied by comparing patients randomised to the home setting with those who chose the home setting.

The results from this design should also indicate any clinical or demographical differences between the different populations at baseline and produce estimates of likely rates of uptake of the different settings to help inform future service provision. This study design would more clearly identify setting-related safety issues (which appear to be one of the key concerns about the implementation of a home or community chemotherapy service). Larger and more generalisable data sets would enable analyses to be made of whether or not setting-related issues that are important to patients, such as waiting times, anxiety or transport, vary according to patient characteristics.

This approach to study design is very similar to one advocated for trials of counselling following mastectomy described in a paper about patient preference and randomisation; this discussion paper also suggested a change-from-baseline approach when analysing some outcomes of non-randomised groups.[79]

Other similar designs include the randomised consent (Zelen) design[83] and the cohort multiple RCT.[84] However, in addition to the lack of patient consent issues to be considered when using these designs, neither design uses a crossover component which, in this area of research, would appear to be the most appropriate option for two reasons.

First, when compared with other designs, fewer patients would need to be randomised to obtain the same number of observations and fewer observations are needed to obtain the same precision in estimation. This is a consequence of patients acting as their own controls and between-patient variation being eliminated.[85] This should help to minimise patient accrual problems.

Second, each patient should experience both settings for an adequate period to enable a more accurate estimate of preference.

Crossover trials have some disadvantages in this area of research: patients must have relatively stable disease states; and dealing with dropouts can be more problematic than with parallel designs. Lack of disease stability was an issue for some of the crossover trials in this review.[29,31,34]

The many methodological issues identified in this review suggest that, whichever design is chosen for future studies, a feasibility study should first be performed (with feasibility outcomes); any resulting larger study should begin with a pilot phase.

The issues identified in this review which led to these recommendations for future research highlight the importance of using systematic reviews to inform the design of new studies.[86]

Another recommendation for further research would be studies of within-setting comparisons; these are absent from the evidence base and it is unclear how a new outpatient facility affects quality of life unless it can be compared with an old facility. Similarly, no studies exist which compare different types of community setting (e.g. community bus vs. GP facility).

Outcome measures

Many studies in this review used validated tools; such tools are often preferred because non-validated scales may produce larger and less reliable effects. Existing validated tools tend to comprise a core set of questions (20 to 30 items) and a number of cancer-specific add-on modules such as the EORTC QLQ-C30, FLIC and Functional Assessment of Cancer Therapy.[87–89] These measures tend to focus heavily on physical functioning, particularly in the case of the EORTC QLQ-C30 and the FLIC, and so may not be responsive to the kind of issues highlighted in the qualitative synthesis (e.g. available time and energy, control over impact of the disease on daily life). Quality-of-life measures sensitive to these issues are needed to ensure that future trials are equipped to detect significant differences where these exist. It may be important to differentiate between patients receiving palliative versus curative treatment; some existing tools offer separate modules to accommodate this. Part of the challenge is that many of these outcome measures were developed to capture the burden of disease and not the burden of treatment.

As an alternative to developing new outcome measures, researchers may find it helpful to consider patient-generated outcome measures. Specifically, Measure Your own Concerns And Wellbeing was developed from the Measure Your Medical Outcome Profile tool for use in cancer treatment centres that provided integrative treatment.[90,91] Validation is ongoing. The innovative use of a patient-generated format, Likert scales and questions about concerns or problems rather than symptoms may make this tool a useful addition to future trials. MYMOP itself has previously been compared with the Short Form questionnaire-36 items, Medical Outcomes Study – 6-item sale, Dartmouth COOP Functional Health Assessment charts and the EQ-5D, and was shown to be both reliable and more sensitive to small changes than the other outcome measures.[91–93]

Similar problems face the assessment of quality of life in paediatric populations; however, a well-validated and relatively sensitive tool is available for use by researchers and was used by one study in this review. The Paediatric Quality of Life (PedsQL) scale is a rigorously developed package of quality-of-life outcome measures that includes the generic core scales (parent and child forms),[94] a family impact module,[95] and several condition-specific add-on modules (including cancer).[96] There has been some work to develop a paediatric-oriented version of the EQ-5D, although this is expected to be less sensitive.[97]

Implications for practice

Considering the difficulties we have identified and reported in assessing the evidence base and developing a decision model, commissioners should consider the issues we have described, alongside more bespoke guidance and support. For example, the C-PORT Chemotherapy Capacity Planning Tool is a web-based tool (owned and operated by the NHS: www.cport.co.uk/Home.aspx?ReturnUrl=%2fdefault.aspx) that simulates the activity of an adult chemotherapy day case service. Within its many functions it provides users with a visual picture of how their particular service operates in terms of capacity and demand, resource utilisation and patient delays, and enables users to model the effects of potential change

(to help to avoid bottlenecks) and plan for the introduction of new services. Our survey suggests that some organisations use settings other than outpatient for the delivery of treatment and that the mechanisms for delivering treatment in those different settings are variable.

It is not clear what the drivers are that determine the settings that organisations elect to offer. However, these drivers are likely to be a key influence in the way in which services are delivered. Capacity is clearly an issue across the NHS. Dealing with capacity through service reconfiguration is a local issue, dependent on local needs and current service configuration. Patient choice may be a driver in some areas, but it is unclear from the evidence we identified where choice fits into service configuration. In some situations, patients will have choices regarding setting; in others, choice will be dictated by which service is available.

It is likely that service configuration is driven by capacity in areas such as outpatient clinics and pharmacy. Patient choice may then be made available, if feasible, within the service configuration. Other factors, such as VAT exemption on drugs prepared and delivered outside the hospital setting, loss of outpatient tariffs should a service be moved to the home/community and the increasing number of oral treatments, will all impact on local service configuration but are difficult to unpick at a national level.

Research and practice summary points

- Recruitment biases, and problems of recruiting enough willing participants, are unlikely to be overcome in future randomised studies which use conventional study designs. However, randomised crossover trials which are nested within much larger groups of patients (who can choose their preferred setting) are likely to provide results which are relevant to patients seen in clinical practice. Such studies would also help to inform decisions on future service provision.
- Any future studies should begin with feasibility and pilot phases, and aim to use patient questionnaires to record qualitative data. Care should be taken to ensure that the tools used to record other study data are sensitive enough to detect changes in outcome measures which are important to patients.
- Capacity and patient waiting times are among the key issues to consider when evaluating service configuration.

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Advisory group

We would like to thank members of the advisory group who contributed to development of the scope and protocol, answered our questions, attended meetings and reviewed relevant sections of the draft final report. Not all of those listed below were able to participate in all stages of the review.

Dave Ardron, PPI representative.

Pippa Corrie Ph.D. FRCP, Consultant and Associate Lecturer in Medical Oncology, Cambridge University Hospitals NHS Foundation Trust.

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Saskia Syms, PPI representative.

Contributions of authors

All CRD authors contributed to all stages of the systematic review from the development of the protocol to the production of the report.

Mark Corbett (research fellow, CRD) managed the EPPI project software, led on the clinical effectiveness component and shared day-to-day responsibility for the project.

Morag Heirs (research fellow, CRD) took responsibility for project software and co-ordination of the final report, maintained contact with the advisory group members, devised the current provision surveys, led on the qualitative synthesis component and shared day-to-day responsibility for the project.

Micah Rose (research fellow, CRD) analysed the current provision surveys and contributed to the modelling section.

Alison Smith (research fellow, CRD) contributed to the review of economic evaluations.

Lisa Stirk (information specialist, CRD) devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report.

Gerry Richardson (senior research fellow, Centre for Health Economics) provided expertise and advice for the economic components of the project as part of the extended project group, and commented on the protocol and drafts of the report.

Daniel Stark (senior lecturer in cancer medicine at the University of Leeds) provided clinical expertise and advice as part of the extended project group. He also commented on the protocol and drafts of the report.

Daniel Swinson (consultant medical oncologist, St James's Institute of Oncology) provided clinical expertise and advice as part of the extended project group. He also commented on drafts of the report.

Dawn Craig (research fellow, CRD) contributed to all stages of the review, commented on drafts of the report and took overall responsibility for the economic components of the project.

Alison Eastwood (senior research fellow, CRD) contributed to all stages of the review, commented on drafts of the report and took overall responsibility for the project.

References

1. Young AM, Kerr DJ. Home delivery: chemotherapy and pizza? Evidence on safety and acceptability of home chemotherapy is growing. *BMJ* 2001;**322**:809–10. http://dx.doi.org/10.1136/bmj.322.7290.809
2. Boothroyd L, Lehoux P. *Home-Based Chemotherapy for Cancer: Issues for Patients, Caregivers and the Health Care System*. Montreal, QC: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS); 2004.
3. Department of Health. *Chemotherapy Services in the Community – A Guide for PCTs*. London: Department of Health; 2010. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_112586 (accessed 12 March 2013).
4. Corrie PG, Moody AM, Armstrong G, Nolasco S, Lao-Sirieix S, Bavister L, *et al.* Is community treatment best? A randomised trial comparing delivery of cancer treatment in the hospital, home and GP surgery. *Br J Cancer* 2013;**109**:1549–55. http://dx.doi.org/10.1038/bjc.2013.414
5. Department of Health. *NHS 2010–2015: From Good to Great. Preventative, People-Centred, Productive*. London: The Stationery Office; 2009.
6. Department of Health. *Cancer Reform Strategy*. London: Department of Health; 2007.
7. National Chemotherapy Advisory Group. *Chemotherapy Services in England: Ensuring Quality and Safety*. London: National Chemotherapy Advisory Group; 2009.
8. National Audit Office. *Delivering the Cancer Reform Strategy*. London: The Stationery Office; 2010.
9. NHS England. *The Latest on NHS England's Five-Year Strategy for Specialised Services – James Palmer*. NHS England; 2014. URL: www.england.nhs.uk/2014/03/03/james-palmer (accessed 3 March 2014).
10. Clive S, Baird R, Waterston A, Darby S, Newsom-Davis T, Swinson D. *Differing Methods of Delivering Chemotherapy and Managing Toxicities across the UK: Summary Paper from the Association of Cancer Physicians New Consultants Group Workshop*. 7th NCRI Cancer Conference, Liverpool, UK, 6–9 November 2011. URL: http://conference.ncri.org.uk/abstracts/2011/abstracts/B109.html (accessed 26 February 2014).
11. Pope C, Mays N, Popay J. Mixed Approaches to Evidence Synthesis. In Pope C, Mays N, Popay J, editors. *Synthesising Qualitative and Quantitative Evidence: A Guide to Methods*. Maidenhead: Open University Press; 2007.
12. Centre for Reviews and Dissemination. *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care*. York: CRD, University of York; 2009. URL: www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf (accessed 26 February 2014).
13. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. http://dx.doi.org/10.1136/bmj.d5928
14. Corbett MS, Higgins JPT, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Res Syn Meth* 2014;**5**:79–85. http://dx.doi.org/10.1002/jrsm.1090
15. Reeves BC, Higgins JPT, Ramsay C, Shea B, Tugwell P, Wells GA. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. *Res Syn Meth* 2013;**4**:1–11. http://dx.doi.org/10.1002/jrsm.1068

16. Higgins JPT, Ramsay C, Reeves BC, Deeks JJ, Shea B, Valentine JC, *et al.* Issues relating to study design and risk of bias when including non-randomized studies in systematic reviews on the effects of interventions. *Res Syn Meth* 2013;**4**:12–25. http://dx.doi.org/10.1002/jrsm.1056

17. Valentine JC, Thompson SG. Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions. *Res Syn Meth* 2013;**4**:26–35. http://dx.doi.org/10.1002/jrsm.1064

18. Wells GA, Shea B, Higgins JPT, Sterne J, Tugwell P, Reeves BC. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. *Res Syn Meth* 2013;**4**:63–77. http://dx.doi.org/10.1002/jrsm.1077

19. Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration; 2011. URL: www.cochrane-handbook.org (accessed 26 February 2014).

20. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;**313**:275–83. http://dx.doi.org/10.1136/bmj.313.7052.275

21. Mays N, Pope C. Qualitative research in health care: assessing quality in qualitative research. *BMJ* 2000;**320**:50–2. http://dx.doi.org/10.1136/bmj.320.7226.50

22. Mays N, Pope C. Quality in Qualitative Health Research. In Mays N, Pope C, editors. *Qualitative Research in Health Care*. London: BMJ Books; 2000. pp. 89–102.

23. Spencer L, Ritchie J, Lewis J, Dillon L. *Quality in Qualitive Evaluation: A Framework for Assessing Research Evidence*. London: Cabinet Office; 2003. URL: www.civilservice.gov.uk/wp-content/uploads/2011/09/a_quality_framework_tcm6–38740.pdf (accessed 13 May 2013).

24. Taylor HJ. *Multimethod Analysis of NHS Policy for the Development of New Services for Ambulatory Cancer Care*. Ph.D. thesis. London: University of London; 2008.

25. Noblit G, Hare R. *Meta-Ethnography: Synthesising Qualitative Studies*. Newbury Park: Sage; 1988.

26. Britten N, Campbell R, Pope C, Donovan J, Morgan M, Pill R. Using meta ethnography to synthesise qualitative research: a worked example. *J Health Serv Res Policy* 2002;**7**:209–15. http://dx.doi.org/10.1258/135581902320432732

27. Chen JT, Hasuimi K. Differences in the patient anxiety, quality of life (QOL) and nursing efficacy at the first course of chemotherapy infused at home and in hospital. *Int J Gynecol Cancer* 1999;**9**(Suppl. 1):117.

28. Christiansen B, Rishoj A, Jensen BV, Larsen FO, Nielsen D. A randomised crossover trial to determine safety, quality of life and economic consequences of home-based chemotherapy. *Eur J Cancer* 2011;**47**:S294. http://dx.doi.org/10.1016/S0959-8049(11)71317-X

29. Pace E, Dennison S, Morris J, Barton A, Pritchard C, Rule SA. Chemotherapy in the community: what do patients want? *Eur J Cancer Care* 2009;**18**:209–15. http://dx.doi.org/10.1111/j.1365-2354.2008.01051.x

30. Hall M, Lloyd H. Evaluating patients' experiences of home and hospital chemotherapy. *Cancer Nursing Practice* 2008;**7**:35–8. http://dx.doi.org/10.7748/cnp2008.02.7.1.35.c6469

31. King MT, Hall J, Caleo S, Gurney HP, Harnett PR. Home or hospital? An evaluation of the costs, preferences, and outcomes of domiciliary chemotherapy. *Int J Health Serv* 2000;**30**:557–79. http://dx.doi.org/10.2190/CY03-EV15-K38Y-X4AA

32. Rischin D, White MA, Matthews JP, Toner GC, Watty K, Sulkowski AJ, *et al.* A randomised crossover trial of chemotherapy in the home: patient preferences and cost analysis. *Med J Aust* 2000;**173**:125–7.

33. Stevens B, Croxford R, McKeever P, Yamada J, Booth M, Daub S, *et al.* Hospital and home chemotherapy for children with leukemia: a randomized cross-over study. *Pediatr Blood Cancer* 2006;**47**:285–92. http://dx.doi.org/10.1002/pbc.20598

34. Remonnay R, Devaux Y, Chauvin F, Dubost E, Carrere MO. Economic evaluation of antineoplastic chemotherapy administered at home or in hospitals. *Int J Technol Assess Health Care* 2002;**18**:508–19.

35. Borras JM, Sanchez-Hernandez A, Navarro M, Martinez M, Mendez E, Ponton JLL, *et al.* Compliance, satisfaction, and quality of life of patients with colorectal cancer receiving home chemotherapy or outpatient treatment: a randomised controlled trial. *BMJ* 2001;**322**:826–8. http://dx.doi.org/10.1136/bmj.322.7290.826

36. NHS Bristol. *Evaluation Report of the Choice of Chemotherapy Pilot*. London: Department of Health; 2010.

37. Pong RW, Irvine A, McChesney C, DesRochers C, Blanco H, Valiquette A. *Impact Assessment of an Outreach Chemotherapy Program in Northeastern Ontario*. Sudbury, ON: Centre for Rural and Northern Health Research, Laurentian University; 2000.

38. Hansson H, Kjaergaard H, Johansen C, Hallstrom I, Christensen J, Madsen M, *et al.* Hospital-based home care for children with cancer: feasibility and psychosocial impact on children and their families. *Pediatr Blood Cancer* 2013;**60**:865–72. http://dx.doi.org/10.1002/pbc.24474

39. Mitchell T. *Chemotherapy Closer to Home: Patients' Perspectives of Receiving Chemotherapy in Outpatient Clinic and/or a Unique Mobile Chemotherapy Unit*. Bristol: University of the West of England; 2011. URL: http://eprints.uwe.ac.uk/15857 (accessed 30 August 2013).

40. Barker C. A toxicity audit for patients receiving chemotherapy at a clinic or at home. *Cancer Nurs Pract* 2006;**5**:33–9. http://dx.doi.org/10.7748/cnp2006.11.5.9.33.c7588

41. Frølund J. [Home chemotherapy for bone marrow cancer patients – a quantitative study of how patients experience treatment at home.] *Sygeplejersken* 2011;**111**:69–72.

42. Grusenmeyer PA, Gralla RJ, Trapani MM, Bateman MM. Alternatives to inpatient care: a cost comparison of home versus outpatient clinic care for chemotherapy administration and supportive care measures. *Proc Am Soc Clin Oncol* 1996;**15**:324, abstract 926.

43. Herth KA. The relationship between level of hope and level of coping response and other variables in patients with cancer. *Oncol Nurs Forum* 1989;**16**:67–72.

44. Ingleby S, Barnwell J, Baker J, Harvey P, Kerr D, Law V, *et al.* A pilot study of a feasibility and economic analysis of home based chemotherapy in ad-vanced colorectal cancer. *Eur J Cancer* 1999;**35**:S70. http://dx.doi.org/10.1016/S0959-8049(99)80647-9

45. Lowenthal RM, Piaszczyk A, Arthur GE, O'Malley S. Home chemotherapy for cancer patients: cost analysis and safety. *Med J Aust* 1996;**165**:184–7.

46. Payne SA. A study of quality of life in cancer patients receiving palliative chemotherapy. *Soc Sci Med* 1992;**35**:1505–9. http://dx.doi.org/10.1016/0277-9536(92)90053-S

47. Satram-Hoang S, Reyes C. Is there a difference in treatment patterns among follicular lymphoma patients receiving care in the outpatient hospital versus the community clinic setting? *Blood* 2011;**118**:abstract 3134.

48. Souadjian JV, Bhaskar B, Briscoe KE, Opfell RW, Agopian JM. Home chemotherapy (CT): safety and cost-effectiveness. *Proc Am Soc Clin Oncol* 1992;**11**:410.

49. Vergnenègre A, Decroisette C, Vincent F, Dalmay F, Melloni B, Bonnaud F, *et al.* [Economic analysis of home based versus hospital outpatient chemotherapy in stage IV non small cell lung cancer.] *Rev Mal Respir* 2006;**23**:255–63. http://dx.doi.org/10.1016/S0761-8425(06)71575-3

50. Mitchell T. Patients' experiences of receiving chemotherapy in outpatient clinic and/or onboard a unique nurse-led mobile chemotherapy unit: a qualitative study. *Eur J Cancer Care* 2013;**22**:430–9. http://dx.doi.org/10.1111/ecc.12044

51. Iredale R, Hilgart J, Hayward J. Patient perceptions of a mobile cancer support unit in South Wales. *Eur J Cancer Care* 2011;**20**:555–60. http://dx.doi.org/10.1111/j.1365-2354.2011.01247.x

52. The Christie Charitable Fund. *Mobile Chemotherapy – Transforming the Lives of Cancer Patients*. Manchester: The Christie Charitable Fund; 2014. URL: www.christie.nhs.uk/the-christie-charity/current-appeals/mobile-chemotherapy.aspx (accessed 31 March 2014).

53. Hope for Tomorrow. *Hope for Tomorrow: Bringing Cancer Treatment Closer to Home*. Upton Lodge: Hope for Tomorrow. URL: www.hopefortomorrow.org.uk/ (accessed 31 March 2014).

54. King MT, Hall JP, Harnett PR. A randomised crossover trial of chemotherapy in the home: patient preferences and cost analysis. *Med J Aust* 2001;**174**:312; author reply 312–13.

55. Stevens B, McKeever P, Law MP, Booth M, Greenberg M, Daub S, *et al.* Children receiving chemotherapy at home: perceptions of children and parents. *J Pediatr Oncol Nurs* 2006;**23**:276–85. http://dx.doi.org/10.1177/1043454206291349

56. Stevens B, McKeever P, Booth M, Greenberg M, Daub S, Gafni A, *et al.* Home chemotherapy for children with cancer: perspectives from health care professionals. *Health Soc Care Community* 2004;**12**:142–9. http://dx.doi.org/10.1111/j.0966-0410.2004.00480.x

57. Bakker DA, DesRochers C, McChesney C, Fitch M, Bennett J. Community cancer clinics: patients' perspectives. *Support Care Cancer* 2001;**9**:234–40. http://dx.doi.org/10.1007/s005200000226

58. Smith SM, Campbell NC. Provision of oncology services in remote rural areas: a Scottish perspective. *Eur J Cancer Care* 2004;**13**:185–92. http://dx.doi.org/10.1111/j.1365-2354.2003.00472.x

59. Butler MC. Families' responses to chemotherapy by an ambulatory infusion pump . . . at home. *Nurs Clin North Am* 1984;**19**:139–44.

60. Crisp N. *Chemotherapy at Home: Keeping Patients in their 'Natural Habitat'*. Ph.D. thesis. Edmonton, AB: University of Alberta; 2010.

61. Hansson H. *Hospital-Based Home Care for Children with Cancer*. Ph.D. thesis. Copenhagen: University of Copenhagen; 2011.

62. Kelly D, Pearce S, Butters E, Stevens W, Layzell S. Achieving change in the NHS: a study to explore the feasibility of a home-based cancer chemotherapy service. *Int J Nurs Stud* 2004;**41**:215–24. http://dx.doi.org/10.1016/j.ijnurstu.2003.05.002

63. McIlfatrick S, Sullivan K, McKenna H, Parahoo K. Patients' experiences of having chemotherapy in a day hospital setting. *J Adv Nurs* 2007;**59**:264–73. http://dx.doi.org/10.1111/j.1365-2648.2007.04324.x

64. Hjorleifsdottir E, Hallberg IR, Gunnarsdottir ED, Bolmsjo IA. Living with cancer and perception of care: Icelandic oncology outpatients, a qualitative study. *Support Care Cancer* 2008;**16**:515–24. http://dx.doi.org/10.1007/s00520-007-0333-9

65. Heatherwood and Wexham Park Hospitals NHS Foundation Trust. *New Chemo Suite Officially Opened by its Namesake*. Press release, 24 September 2013. URL: www.heatherwoodandwexham.nhs.uk/news/new-chemo-suite-officially-opened-by-its-namesake (accessed 4 March 2014).

66. Walker L. Singer Joe McElderry Opens New Shotley Bridge Chemo Unit. *The Chronicle*, 26 June 2013. URL: www.chroniclelive.co.uk/news/health/singer-joe-mcelderry-opens-new-4711701 (accessed 4 March 2014).

67. Hansson H, Kjaergaard H, Schmiegelow K, Hallstrom I. Hospital-based home care for children with cancer: a qualitative exploration of family members' experiences in Denmark. *Eur J Cancer Care* 2012;**21**:59–66. http://dx.doi.org/10.1111/j.1365-2354.2011.01280.x

68. HM Revenue and Customs. *Notice 701/57 Health Professionals and Pharmaceutical Products*. London: HM Revenue and Customs; 2012.

69. Bupa. *Chemotherapy at Home*. URL: www.bupa.co.uk/healthcare-providers/home-healthcare/what-we-do/home-chemotherapy (accessed 23 January 2014).

70. Bupa. *Home Oncology Service: Supported Regimes and Treatments*. URL: www.bupa.co.uk/jahia/webdav/site/bupacouk/shared/Documents/PDFs/healthcare-professionals/bupa-home-healthcare/A-Z%20Supported%20treatments.pdf (accessed 23 January 2014).

71. Ingleby S, Baker J, Young A, Kerr D. Health economic analysis of home based vs. hospital based chemotherapy: discussion of results. *Br J Cancer* 1999;**80**:111.

72. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal 2013*. London: NICE; 2013. URL: www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf (accessed 26 February 2014).

73. Office for National Statistics. *Cancer Survival in England: Patients Diagnosed 2007–2011 and Followed up to 2012*. ONS; 2013. URL: www.ons.gov.uk/ons/publications/re-reference-tables.html?edition = tcm%3A77–320365 (accessed 26 November 2013).

74. Department of Health. *NHS Reference Costs: Financial Year 2011 to 2012*. London: Department of Health; 2012. URL: www.gov.uk/government/publications/2010–11-reference-costs-publication (accessed 28 March 2014).

75. Curtis L. *Unit Costs of Health and Social Care 2012*. Canterbury: Personal Social Services Research Unit, University of Kent; 2012. URL: www.gov.uk/government/publications/2010–11-reference-costs-publication (accessed 28 March 2014).

76. Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, *et al. Methods for the Estimation of the NICE Cost-Effectiveness Threshold: Revised Report Following Referees' Comments*. York: Centre for Health Economics, University of York; 2013. URL: www.york.ac.uk/media/che/documents/papers/researchpapers/CHE%20Research%20Paper%2081%20%28June%202013%29.pdf (accessed 26 February 2014).

77. van den Berg B, Gafni A, Portrait F. *Attributing a Monetary Value to Patients' Time: A Contingent Valuation Approach*. York: Centre for Health Economics, University of York; 2013. URL: www.york.ac.uk/media/che/documents/papers/researchpapers/CHERP90_monetary_value_patient_time_contingent_valuation.pdf (accessed 26 February 2014).

78. McCambridge J, Kypri K, Elbourne D. In randomization we trust? There are overlooked problems in experimenting with people in behavioral intervention trials. *J Clin Epidemiol* 2014;**67**:247–53. http://dx.doi.org/10.1016/j.jclinepi.2013.09.004

79. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. *BMJ* 1989;**299**:313–15. http://dx.doi.org/10.1136/bmj.299.6694.313

80. Schroen AT, Petroni GR, Wang H, Gray R, Wang XF, Cronin W, *et al.* Preliminary evaluation of factors associated with premature trial closure and feasibility of accrual benchmarks in phase III oncology trials. *Clin Trials* 2010;**7**:312–21. http://dx.doi.org/10.1177/1740774510374973

81. Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, Wilson K, *et al.* Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Oncol* 2006;**7**:141–8. http://dx.doi.org/10.1016/S1470-2045(06)70576-9

82. Bazian Ltd. *Home Chemotherapy*. London: Bazian Ltd; 2010. URL: www.bupa.com/media/357902/bazian_evidence_review_full_report-_final.pdf (accessed 28 May 2013).

83. Homer CS. Using the Zelen design in randomized controlled trials: debates and controversies. *J Adv Nurs* 2002;**38**:200–7. http://dx.doi.org/10.1046/j.1365-2648.2002.02164.x

84. Relton C, Torgerson D, O'Cathain A, Nichol J. Rethinking pragmatic randomised controlled trials: introducing the 'cohort multiple randomised controlled trial' design. *BMJ* 2010;**340**:c1066. http://dx.doi.org/10.1136/bmj.c1066

85. Senn S. *Cross-Over Trials in Clinical Research*. Chichester: Wiley; 2002. http://dx.doi.org/10.1002/0470854596

86. Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. *Lancet* 2010;**376**:20–1. http://dx.doi.org/10.1016/S0140-6736(10)61045-8

87. European Organisation for Research and Treatment of Cancer. *EORTC QLQ-C30*. URL: http://groups.eortc.be/qol/eortc-qlq-c30 (accessed 27 March 2014).

88. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: the Functional Living Index-Cancer: development and validation. *J Clin Oncol* 1984;**2**:472–83.

89. FACITOrg. *Functional Assessment of Cancer Therapy (FACT-G)*. URL: www.facit.org/FACITOrg/Questionnaires (accessed 31 March 2014).

90. Paterson C, Thomas K, Manasse A, Cooke H, Peace G. Measure Yourself Concerns and Wellbeing (MYCaW): an individualised questionnaire for evaluating outcome in cancer support care that includes complementary therapies. *Complement Ther Med* 2007;**15**:38–45. http://dx.doi.org/10.1016/j.ctim.2006.03.006

91. Paterson C. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. *BMJ* 1996;**312**:1016–20. http://dx.doi.org/10.1136/bmj.312.7037.1016

92. Paterson C. Seeking the patient's perspective: a qualitative assessment of EuroQol, COOP-WONCA charts and MYMOP. *Qual Life Res* 2004;**13**:871–81. http://dx.doi.org/10.1023/B:QURE.0000025586.51955.78

93. Paterson C, Langan CE, McKaig GA, Anderson PM, Maclaine GD, Rose LB, *et al.* Assessing patient outcomes in acute exacerbations of chronic bronchitis: the measure your medical outcome profile (MYMOP), medical outcomes study 6-item general health survey (MOS-6 A) and EuroQol (EQ-5D). *Qual Life Res* 2000;**9**:521–7. http://dx.doi.org/10.1023/A:1008930521566

94. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;**39**:800–12. http://dx.doi.org/10.1097/00005650-200108000-00006

95. Varni JW, Sherman SA, Burwinkle TM, Dickinson PE, Dixon P. The PedsQL Family Impact Module: preliminary reliability and validity. *Health Qual Life Outcomes* 2004;**2**:55. http://dx.doi.org/10.1186/1477-7525-2-55

96. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer* 2002;**94**:2090–106. http://dx.doi.org/10.1002/cncr.10428

97. Hennessy S, Kind P, Group OR. *Measuring Health Status in Children: Developing and Testing a Child-Friendly Version of EQ-5D*. York: Centre for Health Economics, University of York; 2002.

98. Corrie PG, Moody M, Wood V, Bavister L, Prevost T, Parker RA, *et al.* Protocol for the OUTREACH trial: a randomised trial comparing delivery of cancer systemic therapy in three different settings: patient's home, GP surgery and hospital day unit. *BMC Cancer* 2011;**11**:467. http://dx.doi.org/10.1186/1471-2407-11-467

99. Corrie P. *Is Hospital the Best Location to Deliver Cancer Therapy? Interim Results of the Outreach Randomised Clinical Trial*. Liverpool: 7th NCRI Cancer Conference; 2011. URL: www.ncri.org.uk/ncriconference/2011abstracts/abstracts/LB32.html (accessed 28 May 2013).

100. Corrie P, Moody M, Wood V, Nolasco S, Armstrong G, Lao-Sirieix S, *et al. Community Cancer Treatment: Final Results of the Outreach Randomised Clinical Trial*. Liverpool: 8th NCRI Cancer Conference; 2012. URL: www.ncri.org.uk/ncriconference/2012abstracts/abstracts/LB40.html (accessed 28 May 2014).

101. Caleo S, King M, Cameron S, Hall J. *An Evaluation of Domiciliary Chemotherapy*. Clinical Oncological Society of Australia (COSA) 23rd Annual Scientific Meeting, November 1996, Brisbane, Australia.

102. Pace E, Dennison S, Morris J, Rule S, Pritchard C, Barton A, *et al.* A study to compare patient satisfaction with location of chemotherapy: community hospital versus cancer centre. *EJC Suppl* 2007;**5**:461. http://dx.doi.org/10.1016/S1359-6349(07)71684-1

103. Remonnay R, Devaux Y, Chauvin F, Dubost E, Carrere MO. [Developing home-care hospitalization: cost evaluation and assessment criteria. The case of anticancer chemotherapy.] *Rev Epidemiol Sante Publique* 2003;**51**:649–52.

104. Breitfeld PP. Belief in home chemotherapy. *Pediatr Blood Cancer* 2006;**47**:237–8. http://dx.doi.org/10.1002/pbc.20679

105. Hansson H, Johansen C, Hallstrom I, Kjaergaard H, Schmiegelow K. Hospital-based home care for children with cancer. *Pediatr Blood Cancer* 2010;**55**:838–9.

106. Hansson H, Johansen C, Hallstrom I, Kjaergaard H, Schmiegelow K. Hospital-based home care for children with cancer – health related quality of life and the psychosocial impact on the family. *Pediatr Blood Cancer* 2012;**59**:1121.

107. Herth KA. *The Relationship Between the Level of Hope and the Level of Coping Response in Cancer Patients*. Ph.D. thesis. Denton, TX: Texas Woman's University; 1987.

108. Payne SA. Coping with palliative chemotherapy. *J Adv Nurs* 1990;**15**:652–8. http://dx.doi.org/10.1111/j.1365-2648.1990.tb01887.x

109. Hjorleifsdottir E, Rahm Hallberg I, Agren Bolmsjo I, Gunnarsdottir ED. Icelandic cancer patients receiving chemotherapy or radiotherapy: does distance from treatment center influence distress and coping? *Cancer Nurs* 2007;**30**:E1–10. http://dx.doi.org/10.1097/01.NCC.0000300161.06016.a9

110. Taylor H, Ireland J, Duggan C, Bates I. Home chemotherapy – a feasibility study. *Br J Home Healthc* 2007;**3**:4–5.

Appendix 1 Search strategies

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations

URL: http://ovidsp.ovid.com

Date range: 1946 to week 2 March 2013.

Date searched: 25 March 2013.

Records found: 1564.

Update

Date range: 1946 to week 3 October 2013.

Date searched: 29 October 2013.

Records found: 1748.

Search strategy

Cancer terms	1. exp neoplasms/ (2,406,640) 2. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (2,073,583) 3. oncologic nursing/ (6088) 4. or/1-3 (2,889,785)
Chemotherapy terms	1. drug therapy/ (33,151) 2. Antineoplastic Combined Chemotherapy Protocols/ (97,247) 3. chemotherapy, adjuvant/ or consolidation chemotherapy/ or maintenance chemotherapy/ (27,648) 4. administration, intravenous/ or infusions, intravenous/ (46,068) 5. chemotherapy.ti,ab. (223,465) 6. systemic therapy.ti,ab. (5856) 7. intravenous drug therapy.ti,ab. (39) 8. adjuvant therapy.ti,ab. (14,653) 9. or/5-12 (357,679)
Home care terms	1. home care services/ or home care services, hospital-based/ (28,037) 2. *Outpatients/ (2136) 3. *Ambulatory Care/ (14,592) 4. *ambulatory care facilities/ or *outpatient clinics, hospital/ (13,416) 5. community health services/ or community health nursing/ or community health centers/ (47,800) 6. general practitioners/ or physicians, family/ or physicians, primary care/ (16,406) 7. general practice/ or family practice/ (61,185) 8. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (42,475) 9. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (15,680) 10. or/14-22 (207,550)
Cancer + chemo + home care	1. 4 and 13 and 23 (1144)

Home chemo terms	1. home infusion therapy/ (579) 2. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (719) 3. (chemotherapy adj6 service$).ti,ab. (184) 4. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (19) 5. (self-infusion adj6 home).ti,ab. (21) 6. home infusion.ti,ab. (254) 7. or/25-30 (1591)
Cancer + home chemo	1. 4 and 31 (751)
Set 24 OR Set 31	1. 24 or 32 (1595)
Exclude animal-only studies	1. exp animals/ not humans/ (3,782,734) 2. 33 not 34 (1564)
Final results set	

Key:

/ = indexing term (MeSH heading)

exp = exploded MeSH heading

* = major MeSH heading

$ = truncation

.ti,ab. = terms in either title or abstract fields

Adj6 = terms within six words of each other (any order).

Other strategies

Allied and Complementary Medicine Database

URL: http://ovidsp.ovid.com

Date range: 1985 to March 2013.

Date searched: 25 March 2013.

Records found: 44.

Search strategy

1. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (13,694)
2. chemotherapy.ti,ab. (1083)
3. systemic therapy.ti,ab. (30)
4. intravenous drug therapy.ti,ab. (0)
5. adjuvant therapy.ti,ab. (76)
6. or/2-5 (1167)
7. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (2940)
8. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (1167)

9. 7 or 8 (3782)
10. 1 and 6 and 9 (26)
11. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (21)
12. (chemotherapy adj6 service$).ti,ab. (8)
13. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (1)
14. (self-infusion adj6 home).ti,ab. (0)
15. home infusion.ti,ab. (8)
16. or/11-15 (34)
17. 1 and 16 (31)
18. 10 or 17 (44)

Key:

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj6 = terms within six words of each other (any order).

British Nursing Index

URL: http://proquest.com

Date range: 1994 to March 2013.

Date searched: 25 March 2013.

Records found: 65.

Search strategy

S1 TI,AB(cancer* or neoplas* or tumor* or tumour* or malignan* or oncolog* or carcinoma*) 12003

S2 TI,AB(chemotherapy) (1121)

S3 TI,AB("systemic therapy") (15)

S4 TI,AB("intravenous drug therapy") (6)

S5 TI,AB("adjuvant therapy") (39)

S6 S2 or s3 or s4 or s5 (1167)

S7 TI,AB((service* or therapy or treatment*) NEAR/6 (home or community or outreach or "out-reach" or ambulatory or domicil*)) (2719)

S8 TI,AB("hospital at home" or "hospital in the home" or "own home*" or "home care" or homecare or "closer to home") (1084)

S9 S7 or s8 (3566)

S10 s1 and s6 and s9 (22)

S11 TI,AB(chemotherapy NEAR/6 (home or community or outreach or "out-reach" or ambulatory or domicil*)) (56)

S12 TI,AB(chemotherapy NEAR/6 service*) (37)

S13 TI,AB(chemotherapy NEAR/6 ("general practitioner*" or "family practitioner*" or "family doctor*" or "primary care physician*")) (0)

S14 TI,AB("self-infusion" NEAR/6 home) (0)

S15 TI,AB("home infusion") (2)

S16 s11 or s12 or s13 or s14 or s15 (82)

S17 s1 and s16 (61)

S18 s10 or s17 (65)

Key:

TI,AB = terms in either title or abstract fields

* = truncation

NEAR/6 = terms within six words of each other (any order)

" " = phrase search.

Cumulative Index to Nursing and Allied Health Literature

URL: http://health.ebsco.com

Date range: 1982 to March 2013.

Date searched: 25 March 2013.

Records found: 884.

Update

Date range searched: 1982 to March 2013.

Date searched: 29 October 2013.

Records found: 1069.

Search strategy

S1 (MH "Neoplasms+") (162,398)

S2 cancer* or neoplas* or tumor* or tumour* or malignan* or oncolog* or carcinoma* (201,467)

S3 (MH "Oncologic Nursing") OR (MH "Pediatric Oncology Nursing") (10,675)

S4 S1 OR S2 OR S3 (216,493)

S5 (MH "Chemotherapy, Adjuvant") OR (MH "Chemotherapy, Cancer") (11,453)

S6 (MH "Administration, Intravenous") OR (MH "Infusions, Intravenous") (6862)

S7 chemotherapy (21,389)

S8 "systemic therapy" (967)

S9 "intravenous drug therapy" (45)

S10 "adjuvant therapy" (1311)

S11 S5 OR S6 OR S7 OR S8 OR S9 OR S10 (29,231)

S12 (MH "Home Health Care") (13,640)

S13 (MH "Home Nursing, Professional") (6375)

S14 (MH "Community Health Nursing") OR (MH "Community Health Services") OR (MH "Community Health Centers") (29,922)

S15 (MH "Outpatients") (28,597)

S16 (MH "Ambulatory Care") (5611)

S17 (MH "Ambulatory Care Facilities") OR (MH "Ambulatory Care Nursing") (3924)

S18 (MH "Family Practice") (9893)

S19 (MH "Physicians, Family") (7696)

S20 (service* or therapy or treatment*) N6 (home or community or outreach or "out-reach" or ambulatory or domicil*) (32,720)

S21 "hospital at home" or "hospital in the home" or "own home*" or "home care" or homecare or "closer to home" (14,801)

S22 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 (120,856)

S23 S4 AND S11 AND S22 (745)

S24 (MH "Home Intravenous Therapy") (1197)

S25 chemotherapy N6 (home or community or outreach or "out-reach" or ambulatory or domicil*) (214)

S26 chemotherapy N6 service* (77)

S27 chemotherapy N6 ("general practitioner*" or "family practitioner*" or "family doctor*" or "primary care physician*") (4)

S28 "self-infusion" N6 home (3)

S29 "home infusion" (263)

S30 S24 OR S25 OR S26 OR S27 OR S28 OR S29 (1476)

S31 S4 and S30 (320)

S32 S23 OR S31 (884)

Key:

MH = indexing term (MeSH heading)

* = truncation

" " = phrase search

N6 = terms within six words of each other (any order)

ClinicalTrials.gov

URL: www.clinicaltrials.gov

Date searched: 27 March 2013.

Relevant records found: 0.

Search strategy

chemotherapy AND home 154 - none relevant

"ambulatory chemotherapy" (0)

"chemotherapy in the community" (0)

"domiciliary chemotherapy" (0)

"home intravenous therapy" (0)

"self-infusion at home" (0)

"home infusion" 5 - none relevant (0)

"outreach chemotherapy" (0)

"out-reach chemotherapy" (0)

chemotherapy AND "general practice" (9) - none relevant

chemotherapy AND "primary care" (76) - none relevant

Key:

" " = phrase search.

The Cochrane Library

URL: http://onlinelibrary.wiley.com

Date searched: 25 March 2013.

Cochrane Database of Systematic Reviews, Issue 2 of 12, February 2013.

Records found: 2.

Update

Date searched: 29 October 2013.

Cochrane Database of Systematic Reviews, Issue 10 of 12, October 2013.

Records found: 3.

Search strategy

#1 MeSH descriptor: [Neoplasms] explode all trees

#2 cancer* or neoplas* or tumor* or tumour* or malignan* or oncolog* or carcinoma*:ti,ab,kw (Word variations have been searched)

#3 MeSH descriptor: [Oncologic Nursing] this term only

#4 #1 or #2 or #3

#5 MeSH descriptor: [Drug Therapy] this term only

#6 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only

#7 MeSH descriptor: [Chemotherapy, Adjuvant] this term only

#8 MeSH descriptor: [Consolidation Chemotherapy] this term only

#9 MeSH descriptor: [Maintenance Chemotherapy] this term only

#10 MeSH descriptor: [Administration, Intravenous] this term only

#11 MeSH descriptor: [Infusions, Intravenous] this term only

#12 chemotherapy or "systemic therapy" or "intravenous drug therapy" or "adjuvant therapy":ti,ab,kw (Word variations have been searched)

#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Home Care Services] this term only

#15 MeSH descriptor: [Home Care Services, Hospital-Based] this term only

#16 MeSH descriptor: [Outpatients] this term only

#17 MeSH descriptor: [Ambulatory Care] this term only

#18 MeSH descriptor: [Ambulatory Care Facilities] this term only

#19 MeSH descriptor: [Outpatient Clinics, Hospital] this term only

#20 MeSH descriptor: [Community Health Services] this term only

#21 MeSH descriptor: [Community Health Nursing] this term only

#22 MeSH descriptor: [Community Health Centers] this term only

#23 MeSH descriptor: [General Practitioners] this term only

#24 MeSH descriptor: [Physicians, Family] this term only

#25 MeSH descriptor: [Physicians, Primary Care] this term only

#26 MeSH descriptor: [General Practice] this term only

#27 MeSH descriptor: [Family Practice] this term only

#28 service* near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*):ti,ab,kw (Word variations have been searched)

#29 therapy near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*):ti,ab,kw (Word variations have been searched)

#30 treatment* near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*):ti,ab, kw (Word variations have been searched)

#31 "hospital at home" or "hospital in the home" or "own home*" or "home care" or homecare or "closer to home":ti,ab,kw (Word variations have been searched)

#32 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31

#33 #4 and #13 and #32

#34 MeSH descriptor: [Home Infusion Therapy] this term only

#35 chemotherapy near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*):ti, ab,kw (Word variations have been searched)

#36 chemotherapy near/6 service*:ti,ab,kw (Word variations have been searched)

#37 chemotherapy near/6 ("general practitioner*" or "family practitioner*" or "family doctor*" or "family physician*" or "primary care physician*"):ti,ab,kw (Word variations have been searched)

#38 "self-infusion" near/6 home:ti,ab,kw (Word variations have been searched)

#39 "home infusion":ti,ab,kw (Word variations have been searched)

#40 #34 or #35 or #36 or #37 or #38 or #39

#41 #4 and #40

#42 #33 or #41

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

" " = phrase search

:ti,ab,kw = terms in title, abstract or keyword fields

near/6 = terms within six words of each other (any order).

The Cochrane Library

Date searched: 25 March 2013.

- Database of Abstracts of Reviews of Effects: Issue 1 of 4, January 2013.
  - Records found: 9.
- Health Technology Assessment Database: Issue 1 of 4, January 2013.
  - Records found: 2.
- NHS Economic Evaluation Database: Issue 1 of 4, January 2013.
  - Records found: 67.
- Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2013.
  - Records found: 161.
- Cochrane Methodology Register: Issue 3 of 4, July 2012.
  - Records found: 9.

Update

Date searched: 29 October 2013.

- Database of Abstracts of Reviews of Effects: Issue 3 of 4, July 2013.
  - Records found: 9.
- Health Technology Assessment Database: Issue 3 of 4, July 2013.
  - Records found: 2.
- NHS Economic Evaluation Database: Issue 3 of 4, July 2013.
  - Records found: 67.

- Cochrane Central Register of Controlled Trials: Issue 9 of 12, September 2013.
  - Records found: 161.
- Cochrane Methodology Register: Issue 3 of 4, July 2012.
  - Records found: 9.

Search strategy

#1 MeSH descriptor: [Neoplasms] explode all trees

#2 cancer* or neoplas* or tumor* or tumour* or malignan* or oncolog* or carcinoma* (Word variations have been searched)

#3 MeSH descriptor: [Oncologic Nursing] this term only

#4 #1 or #2 or #3

#5 MeSH descriptor: [Drug Therapy] this term only

#6 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only

#7 MeSH descriptor: [Chemotherapy, Adjuvant] this term only

#8 MeSH descriptor: [Consolidation Chemotherapy] this term only

#9 MeSH descriptor: [Maintenance Chemotherapy] this term only

#10 MeSH descriptor: [Administration, Intravenous] this term only

#11 MeSH descriptor: [Infusions, Intravenous] this term only

#12 chemotherapy or "systemic therapy" or "intravenous drug therapy" or "adjuvant therapy" (Word variations have been searched)

#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Home Care Services] this term only

#15 MeSH descriptor: [Home Care Services, Hospital-Based] this term only

#16 MeSH descriptor: [Outpatients] this term only

#17 MeSH descriptor: [Ambulatory Care] this term only

#18 MeSH descriptor: [Ambulatory Care Facilities] this term only

#19 MeSH descriptor: [Outpatient Clinics, Hospital] this term only

#20 MeSH descriptor: [Community Health Services] this term only

#21 MeSH descriptor: [Community Health Nursing] this term only

#22 MeSH descriptor: [Community Health Centers] this term only

#23 MeSH descriptor: [General Practitioners] this term only

#24 MeSH descriptor: [Physicians, Family] this term only

#25 MeSH descriptor: [Physicians, Primary Care] this term only

#26 MeSH descriptor: [General Practice] this term only

#27 MeSH descriptor: [Family Practice] this term only

#28 service* near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*) (Word variations have been searched)

#29 therapy near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*) (Word variations have been searched)

#30 treatment* near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*) (Word variations have been searched)

#31 "hospital at home" or "hospital in the home" or "own home*" or "home care" or homecare or "closer to home" (Word variations have been searched)

#32 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31

#33 #4 and #13 and #32

#34 MeSH descriptor: [Home Infusion Therapy] this term only

#35 chemotherapy near/6 (home or community or outreach or "out-reach" or ambulatory or domicil*) (Word variations have been searched)

#36 chemotherapy near/6 service* (Word variations have been searched)

#37 chemotherapy near/6 ("general practitioner*" or "family practitioner*" or "family doctor*" or "family physician*" or "primary care physician*") (Word variations have been searched)

#38 "self-infusion" near/6 home (Word variations have been searched)

#39 "home infusion" (Word variations have been searched)

#40 #34 or #35 or #36 or #37 or #38 or #39

#41 #4 and #40

#42 #33 or #41

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

" " = phrase search

near/6 = terms within six words of each other (any order).

Conference Proceedings Citation Index – Science (Web of Knowledge)

URL: http://wokinfo.com

Date range: 1990 to March 2013.

Date searched: 25 March 2013.

Records found: 135.

Update

Date range: 1990 to October 2013.

Date searched: 29 October 2013.

Records found: 141.

Search strategy

1 266,359 Topic=(cancer* or neoplas* or tumor* or tumour* or malignan* or oncolog* or carcinoma*)

2 27,630 Topic=(chemotherapy)

3 625 Topic=("systemic therapy")

4 3 Topic=("intravenous drug therapy")

5 1960 Topic=("adjuvant therapy")

6 29,227 #5 OR #4 OR #3 OR #2

7 5659 Topic=((service* or therapy or treatment*) NEAR/6 (home or community or outreach or out-reach or ambulatory or domicil*))

8 1213 Topic=("hospital at home" or "hospital in the home" or "own home*" or "home care" or homecare or "closer to home")

9 6636 #8 OR #7

10 61 #9 AND #6 AND #1

11 119 Topic=(chemotherapy NEAR/6 (home or community or outreach or "out-reach" or ambulatory or domicil*))

12 13 Topic=(chemotherapy NEAR/6 service*)

13 2 Topic=(chemotherapy NEAR/6 ("general practitioner" or "family practitioner*" or "family doctor*" or "family physician*" or "primary care physician*"))

14 2 Topic=("self-infusion" NEAR/6 home)

15 11 Topic=("home infusion")

16 146 #15 OR #14 OR #13 OR #12 OR #11

17 91 #16 AND #1

18 135 #17 OR #10

Key:

TS= topic tag; searches terms in Title, Abstract, Author Keywords and Keywords Plus fields

* = truncation

" " = phrase search

NEAR/6 = terms within six words of each other (any order).

Current Controlled Trials

URL: http://controlled-trials.com/mrct/search.html

Date searched: 27 March 2013.

Relevant records found: 0.

Search strategy

chemotherapy AND home 254 - none relevant

'ambulatory chemotherapy' 0

'chemotherapy in the community' 1 - none relevant

'domiciliary chemotherapy' 0

'home intravenous therapy' 0

'self-infusion at home' 0

'home infusion' 6 - none relevant

'outreach chemotherapy' 0

'out-reach chemotherapy' 0

chemotherapy AND 'general practice' 6 - none relevant

chemotherapy AND 'primary care' 66 - none relevant

Key:

' ' = phrase search

Dissertation Abstracts

URL: www.dialog.com

Date range: 1861 to March 2013.

Date searched: 27 March 2013.

Records found: 24.

Search strategy

S1 47073 (CANCER? OR NEOPLAS? OR TUMOR OR TUMORS OR TUMOUR OR TUMOURS OR MALIGNANT OR MALIGNANCY OR ONCOLOGY OR CARCINOMA?)

S2 3395 CHEMOTHERAPY

S3 54 SYSTEMIC(W)THERAPY

S4 2 INTRAVENOUS(W)DRUG(W)THERAPY

S5 119 ADJUVANT(W)THERAPY

S6 3523 S2 OR S3 OR S4 OR S5

S7 9903 (SERVICE? OR THERAPY OR TREATMENT?)(6N)(HOME OR COMMUNITY - OR OUTREACH OR OUT(W)REACH OR AMBULATORY OR DOMICIL?)

S8 1689 HOSPITAL(W)AT(W)HOME OR HOSPITAL(W)IN(W)THE(W)HOME OR OWN(- W)HOME? OR HOME (W)CARE OR HOMECARE OR CLOSER(W)TO(W)HOME

S9 11189 S7 OR S8

S10 11 S1 AND S6 AND S9

S11 18 CHEMOTHERAPY(6N)(HOME OR COMMUNITY OR OUTREACH OR OUT(W)REACH OR AMBULATORY OR DOMICIL?)

S12 3 CHEMOTHERAPY(6N)SERVICE?

S13 0 CHEMOTHERAPY(6N)(GENERAL(W)PRACTITIONER? OR FAMILY(W)PRACTITIONER? OR FAMILY(W) DOCTOR? OR PRIMARY(W)CARE(W)PHYSICIAN?)

S14 0 SELF(W)INFUSION(6N)HOME

S15 6 HOME(W)INFUSION

S16 27 S11 OR S12 OR S13 OR S14 OR S15

S17 16 S1 AND S16

S18 24 S10 OR S17

Key:

? = truncation

(W) = terms adjacent to each other (same order)

(6N) = terms within 6 words of each other (any order).

EconLit

URL: http://ovidsp.ovid.com

Date range: 1961 to February 2013.

Date searched: 25 March 2013.

Records found: 1.

Search strategy

1. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (1014)
2. chemotherapy.ti,ab. (50)
3. systemic therapy.ti,ab. (3)
4. intravenous drug therapy.ti,ab. (0)
5. adjuvant therapy.ti,ab. (2)
6. or/2-5 (54)
7. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (893)
8. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (345)
9. 7 or 8 (1175)
10. 1 and 6 and 9 (1)
11. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (1)
12. (chemotherapy adj6 service$).ti,ab. (0)
13. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (0)
14. (self-infusion adj6 home).ti,ab. (0)
15. home infusion.ti,ab. (1)
16. or/11-15 (2)
17. 1 and 16 (1)
18. 10 or 17 (1)

Key:

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj6 = terms within six words of each other (any order).

EMBASE

URL: http://ovidsp.ovid.com

Date range: 1974 to 22 March 2013.

Date searched: 25 March 2013.

Records found: 2719.

Update

Date range: 1974 to 28 October 2013.

Date searched: 29 October 2013.

Records found: 2940.

Search strategy

1. exp neoplasm/ (3,205,629)
2. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti, ab. (2,642,872)
3. exp oncology nursing/ (5654)
4. or/1-3 (3,707,658)
5. chemotherapy/ or adjuvant chemotherapy/ or cancer chemotherapy/ or combination chemotherapy/ or consolidation chemotherapy/ or induction chemotherapy/ or maintenance chemotherapy/ or multimodal chemotherapy/ (252,289)
6. antineoplastic agent/ (211,787)
7. chemotherapy.ti,ab. (314,754)
8. systemic therapy.ti,ab. (8828)
9. intravenous drug therapy.ti,ab. (53)
10. adjuvant therapy.ti,ab. (20,039)
11. or/5-10 (580,292)
12. home care/ (45,243)
13. *outpatient/ (6050)
14. *ambulatory care/ or *ambulatory care nursing/ (11,954)
15. *outpatient department/ (11,572)
16. community care/ or community health nursing/ (68,672)
17. general practitioner/ or general practice/ (115,882)
18. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (54,756)
19. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (18,147)
20. or/12-19 (289,243)
21. 4 and 11 and 20 (2138)
22. home intravenous therapy/ (17)
23. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti, ab. (1000)
24. (chemotherapy adj6 service$).ti,ab. (254)
25. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (28)
26. (self-infusion adj6 home).ti,ab. (27)
27. home infusion.ti,ab. (350)
28. or/22-27 (1624)

29. 4 and 28 (954)
30. 21 or 29 (2733)
31. animals/ or nonhumans/ (1,821,160)
32. humans/ (14178823)
33. 31 not (31 and 32) (1,363,257)
34. 30 not 33 (2719)

Key:

/ = indexing term (EMTREE heading)

* = focussed EMTREE heading

exp = exploded EMTREE heading

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj6 = terms within six words of each other (any order).

Google

URL: www.google.com

Date searched: 10 September 2013.

Additional records found: 16.

Checked first 100 hits for all search strings for relevancy.

Search strategy

("home infusion therapy" AND chemotherapy AND (cancer OR neoplasms)) filetype:pdf = 21,000 hits

("home chemotherapy" AND (cancer OR neoplasms)) filetype:pdf = 1160 hits

("chemotherapy at home" AND (cancer OR neoplasms)) filetype:pdf = 4360 hits

("outreach chemotherapy" AND (cancer OR neoplasms)) filetype:pdf = 177 hits

("ambulatory chemotherapy" AND (cancer OR neoplasms)) filetype:pdf = 1190 hits

("hospital at home" AND chemotherapy AND (cancer OR neoplasms)) filetype:pdf = 27,000 hits

("closer to home" AND chemotherapy AND (cancer OR neoplasms)) filetype:pdf = 22,800 hits

Health Management Information Consortium

URL: http://ovidsp.ovid.com

Date range: 1979 to January 2013.

Date searched: 25 March 2013.

Records found: 44.

Search strategy

1. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (12,171)
2. chemotherapy.ti,ab. (542)
3. systemic therapy.ti,ab. (9)
4. intravenous drug therapy.ti,ab. (1)
5. adjuvant therapy.ti,ab. (35)
6. or/2-5 (579)
7. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (9283)
8. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (2469)
9. 7 or 8 (10,981)
10. 1 and 6 and 9 (24)
11. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti, ab. (30)
12. (chemotherapy adj6 service$).ti,ab. (37)
13. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician $ or primary care physician$)).ti,ab. (0)
14. (self-infusion adj6 home).ti,ab. (0)
15. home infusion.ti,ab. (0)
16. or/11-15 (55)
17. 1 and 16 (35)
18. 10 or 17 (44)

Key:

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj6 = terms within six words of each other (any order).

Inside Conferences

URL: www.dialog.com

Date range: 1993 to March 2013.

Date searched: 27 March 2013.

Records found: 25.

Search strategy

S1 113738 (CANCER? OR NEOPLAS? OR TUMOR OR TUMORS OR TUMOUR OR TUMOURS OR MALIGNANT OR MALIGNANCY OR ONCOLOGY OR CARCINOMA?)

S2 10350 CHEMOTHERAPY

S3 97 SYSTEMIC(W)THERAPY

S4 0 INTRAVENOUS(W)DRUG(W)THERAPY

S5 408 ADJUVANT(W)THERAPY

S6 10815 S2 OR S3 OR S4 OR S5

S7 2387 (SERVICE? OR THERAPY OR TREATMENT?)(6N)(HOME OR COMMUNITY - OR OUTREACH OR OUT(W)REACH OR AMBULATORY OR DOMICIL?)

S8 656 HOSPITAL(W)AT(W)HOME OR HOSPITAL(W)IN(W)THE(W)HOME OR OWN(- W)HOME? OR HOME (W)CARE OR HOMECARE OR CLOSER(W)TO(W)HOME

S9 2938 S7 OR S8

S10 12 S1 AND S6 AND S9

S11 24 CHEMOTHERAPY(6N)(HOME OR COMMUNITY OR OUTREACH OR OUT(W)REACH OR AMBULATORY OR DOMICIL?)

S12 3 CHEMOTHERAPY(6N)SERVICE?

S13 0 CHEMOTHERAPY(6N)(GENERAL(W)PRACTITIONER? OR FAMILY(W)PRACTITIONER? OR FAMILY(W) DOCTOR? OR PRIMARY(W)CARE(W)PHYSICIAN?)

S14 2 SELF(W)INFUSION(6N)HOME

S15 12 HOME(W)INFUSION

S16 40 S11 OR S12 OR S13 OR S14 OR S15

S17 18 S1 AND S16

S18 25 S10 OR S17

Key:

? = truncation

(W) = terms adjacent to each other (same order)

(6N) = terms within 6 words of each other (any order).

Inspec

URL: http://ovidsp.ovid.com

Date range: 1969 to week 10 2013.

Date searched: 25 March 2013.

Records found: 4.

Search strategy

1. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (63,025)
2. chemotherapy.ti,ab. (2100)
3. systemic therapy.ti,ab. (40)
4. intravenous drug therapy.ti,ab. (0)
5. adjuvant therapy.ti,ab. (54)
6. or/2-5 (2176)
7. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (5829)

8. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (1339)
9. 7 or 8 (6986)
10. 1 and 6 and 9 (3)
11. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (4)
12. (chemotherapy adj6 service$).ti,ab. (2)
13. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (0)
14. (self-infusion adj6 home).ti,ab. (0)
15. home infusion.ti,ab. (4)
16. or/11-15 (9)
17. 1 and 16 (3)
18. 10 or 17 (4)

Key:

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj6 = terms within six words of each other (any order).

OHE HEED

URL: http://onlinelibrary.wiley.com/book/10.1002/9780470510933

Date searched: 14 May 2013.

Relevant records found: 29.

Search strategy

chemotherapy AND home 52 - 19 relevant

'ambulatory chemotherapy' 2

'chemotherapy in the community' 0

'domiciliary chemotherapy' 1

'home intravenous therapy' 3 - 2 relevant

'self-infusion at home' 0

'home infusion' 13 - 5 relevant

'outreach chemotherapy' 0

'out-reach chemotherapy' 0

chemotherapy AND 'general practice' 3 - 2 relevant

chemotherapy AND 'primary care' 12 - 1 relevant

Key:

' ' = phrase search.

PsycINFO

URL: http://ovidsp.ovid.com

Date range: 1806 to week 3 2013.

Date searched: 25 March 2013.

Records found: 72.

Search strategy

1. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (46,619)
2. chemotherapy.ti,ab. (3347)
3. systemic therapy.ti,ab. (369)
4. intravenous drug therapy.ti,ab. (0)
5. adjuvant therapy.ti,ab. (246)
6. or/2-5 (3906)
7. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (24,037)
8. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (4691)
9. 7 or 8 (27,793)
10. 1 and 6 and 9 (46)
11. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (42)
12. (chemotherapy adj6 service$).ti,ab. (17)
13. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (2)
14. (self-infusion adj6 home).ti,ab. (1)
15. home infusion.ti,ab. (6)
16. or/11-15 (61)
17. 1 and 16 (44)
18. 10 or 17 (72)

Key:

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj6 = terms within six words of each other (any order).

PubMed

URL: www.ncbi.nlm.nih.gov/pubmed

Date range: all dates to 27 March 2012.

Date searched: 27 March 2013.

Records found: 975.

Update

Date range: all dates to 29 October 2012.

Date searched: 29 October 2013.

Records found: 1007.

Search strategy

#1 Search neoplasms[MeSH Terms] 2,415,714

#2 Search ((((((cancer*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR malignan*[Title/Abstract]) OR oncolog*[Title/Abstract]) OR carcinoma*[Title/Abstract] 2,032,899

#3 Search oncologic nursing[mh:noexp] 6072

#4 Search ((#1) OR #2) OR #3 2,923,865

#5 Search drug therapy[mh:noexp] 33,188

#6 Search antineoplastic combined chemotherapy protocols[mh:noexp] 96,554

#7 Search ((chemotherapy, adjuvant[mh:noexp]) OR consolidation chemotherapy[mh:noexp]) OR maintenance chemotherapy[mh:noexp] 27,399

#8 Search infusion, intravenous[mh:noexp] 45,706

#9 Search chemotherapy[Title/Abstract] 225,942

#10 Search "systemic therapy"[Title/Abstract] 5969

#11 Search "intravenous drug therapy"[Title/Abstract] 40

#12 Search "adjuvant therapy"[Title/Abstract] 14,837

#13 Search (((((((#5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12 359,727

#14 Search (home care services[mh:noexp]) OR home care services, hospital based[mh:noexp] 27,991

#15 Search outpatients[majr:noexp] 2120

#16 Search ambulatory care[majr:noexp] 14,543

#17 Search (ambulatory care facilities[majr:noexp]) OR outpatient clinics, hospital[majr:noexp] 13,413

#18 Search ((community health services[mh:noexp]) OR community health nursing[mh:noexp]) OR community health centers[mh:noexp] 47,623

#19 Search ((general practitioners[mh:noexp]) OR physicians, family[mh:noexp]) OR physicians, primary care [mh:noexp] 16,302

#20 Search (general practice[mh:noexp]) OR family practice[mh:noexp] 60,996

#21 Search ((((((((((((((((“home service*”[Title/Abstract]) OR “home therapy”[Title/Abstract]) OR “home treatment*”[Title/Abstract]) OR “community service”[Title/Abstract]) OR “community therapy”[Title/Abstract]) OR “community treatment”[Title/Abstract]) OR “outreach service*”[Title/Abstract]) OR “outreach therapy”[Title/Abstract]) OR “outreach treatment*”[Title/Abstract]) OR “out-reach service*”[Title/Abstract]) OR “out-reach therapy”[Title/Abstract]) OR “out-reach treatment*”[Title/Abstract]) OR “ambulatory service*”[Title/Abstract]) OR “ambulatory therapy”[Title/Abstract]) OR “ambulatory treatment*”[Title/Abstract]) OR “domicil* service*”[Title/Abstract]) OR “domicil* therapy”[Title/Abstract]) OR “domicil* treatment*”[Title/Abstract] 5808

#22 Search (((((“hospital at home”[Title/Abstract]) OR “hospital in the home”[Title/Abstract]) OR “own home*”[Title/Abstract]) OR “home care”[Title/Abstract]) OR homecare[Title/Abstract]) OR “closer to home”[Title/Abstract] 14,748

#23 Search (((((((#14) OR #15) OR #16) OR #17) OR #18) OR #19) OR #20) OR #21) OR #22 180,529

#24 Search ((#4) AND #13) AND #23 845

#25 Search home infusion therapy[mh:noexp] 580

#26 Search (((((“home chemotherapy”[Title/Abstract]) OR “community chemotherapy”[Title/Abstract]) OR “outreach chemotherapy”[Title/Abstract]) OR “out-reach chemotherapy”[Title/Abstract]) OR “ambulatory chemotherapy”[Title/Abstract]) OR “domicil* chemotherapy”[Title/Abstract] 171

#27 Search “chemotherapy service*”[Title/Abstract] 11

#28 Search ((((“general practitioner chemotherapy”[Title/Abstract]) OR “family practitioner chemotherapy”[Title/Abstract]) OR “family doctor chemotherapy”[Title/Abstract]) OR “family physician chemotherapy”[Title/Abstract]) OR “primary care physician chemotherapy”[Title/Abstract] 0

#29 Search “self-infusion at home”[Title/Abstract] 0

#30 Search “home infusion”[Title/Abstract] 259

#31 Search (((((#25) OR #26) OR #27) OR #28) OR #29) OR #30 890

#32 Search (#4) AND #31 238

#33 Search (#24) OR #32 975

Key:

[MeSH Terms] = indexing term (MeSH heading)

[mh:noexp] = non-exploded MeSH heading

[Title/Abstract] = terms in either title or abstract fields

“ ” = phrase search

* = truncation.

Social Policy and Practice

URL: http://ovidsp.ovid.com

Date range: all dates to January 2013.

Date searched: 25 March 2013.

Records found: 3.

Search strategy

1. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or oncolog$ or carcinoma$).ti,ab. (1854)
2. chemotherapy.ti,ab. (42)
3. systemic therapy.ti,ab. (58)
4. intravenous drug therapy.ti,ab. (0)
5. adjuvant therapy.ti,ab. (0)
6. or/2-5 (100)
7. ((service$ or therapy or treatment$) adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (10,540)
8. (hospital at home or hospital in the home or own home$ or home care or homecare or closer to home).ti,ab. (4276)
9. 7 or 8 (13,575)
10. 1 and 6 and 9 (0)
11. (chemotherapy adj6 (home or community or outreach or out-reach or ambulatory or domicil$)).ti,ab. (2)
12. (chemotherapy adj6 service$).ti,ab. (3)
13. (chemotherapy adj6 (general practitioner$ or family practitioner$ or family doctor$ or family physician$ or primary care physician$)).ti,ab. (0)
14. (self-infusion adj6 home).ti,ab. (0)
15. home infusion.ti,ab. (0)
16. or/11-15 (4)
17. 1 and 16 (3)
18. 10 or 17 (3)

Key:

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj6 = terms within six words of each other (any order).

Appendix 2 Studies which investigated only one setting

Home studies (single setting)

Alfieri P, Bertocchi M, Petocchi B, Torelli G, Favale E. Intravenous chemotherapy at home in hematology patients: a report from the A.I.L. hematology home care service in Modena. *Haematologica* 2009;**94**:179.

Anderson H, Addington-Hall JM, Peake MD, McKendrick J, Keane K, Thatcher N. Domiciliary chemotherapy with gemcitabine is safe and acceptable to advanced non-small-cell lung cancer patients: results of a feasibility study. *Br J Cancer* 2003;**89**:2190–6.

Bassot V, Brasnu D, Lacau-St-Guily J, Fabre A, Menard M, Jacquillat C, *et al.* [Chemotherapy at home. A new methodology.] *Ann Otolaryngol Chir Cervicofac* 1986;**103**:77–81.

Brown DF, Muirhead MJ, Travis PM, Vire SR, Weller J, Hauer-Jensen M. Mode of chemotherapy does not affect complications with an implantable venous access device. *Cancer* 1997;**80**:966–72.

Butler MC. Families' responses to chemotherapy by an ambulatory infusion pump . . . at home. *Nurs Clin North Am* 1984;**19**:139–44.

Chen JT, Ida K, Hasumi K, Masubuchi K. [Maintenance of housewife activity and the quality of familiar interactions by home continuous infusion chemotherapy in patients with recurrent gynecological cancer.] *Gan To Kagaku Ryoho* 1991;**18**:2517–22.

Close P, Burkey E, Kazak A, Danz P, Lange B. A prospective, controlled evaluation of home chemotherapy for children with cancer. *Pediatrics* 1995;**95**:896–900.

Crisp N. Chemotherapy at home: keeping patients in their 'natural habitat'. Ph.D. thesis. Edmonton, AB: University of Alberta; 2010.

D'Andrea B, Belliveau D, Birmingham J, Cooper D. High-dose chemotherapy followed by stem cell transplant: the clinic/home care experience. *J Care Manag* 1997;**3**:46–52.

Dahan M, Paule B, Vordos D, Larre S, Salomon L, Yiou R, *et al.* [Home hospitalisation in urological cancer: assessment of the first 5 years and a satisfaction survey.] *Prog Urol* 2007;**17**:855–9.

DeMoss CJ. Giving intravenous chemotherapy at home. *Am J Nurs* 1980;**80**:2188–9.

Frohmüller S, Schlag P, Leucht R, Ophof J, Ruoff G. [Oncologic therapy at home: a trial model.] *Deutsche Medizinische Wochenschrift* 1989;**114**:1055–8.

Guillevic S, Comont T, Khalifa J, Recher C, Adoue D, Ollier S, *et al.* Home azacitidine administration in high risk myelodysplastic syndromes: favorable results of a pilot study in 48 patients. *Blood* 2011;**118**:749.

Hansson H, Kjaergaard H, Johansen C, Hallström I, Christensen J, Madsen M, *et al.* Hospital-based home care for children with cancer: feasibility and psychosocial impact on children and their families. *Pediatr Blood Cancer* 2013;**60**:865–72.

Harrison DE, Fitch MI. Toronto-Sunnybrook Regional Cancer Centre Home Oncology Model Evaluation (H.O.M.E.) pilot program. *Can Oncol Nurs J* 1995;**5**:85–92.

Hooker L, Kohler J. Safety, efficacy, and acceptability of home intravenous therapy administered by parents of pediatric oncology patients. *Med Pediatr Oncol* 1999;**32**:421–6.

Jayabose S, Escobedo V, Tugal O, Nahaczewski A, Donohue P, Fuentes V, *et al.* Home chemotherapy for children with cancer. *Cancer* 1992;**69**:574–9.

Joo EH, Rha SY, Ahn JB, Kang HY. Economic and patient-reported outcomes of outpatient home-based versus inpatient hospital-based chemotherapy for patients with colorectal cancer. *Support Care Cancer* 2011;**19**:971–8.

Lange BJ, Burroughs B, Meadows AT, Burkey E. Home care involving methotrexate infusions for children with acute lymphoblastic leukemia. *J Pediatr* 1988;**112**:492–5.

Lashlee M, O'Hanlon Curry J. Pediatric home chemotherapy: infusing 'quality of life'. *J Pediatr Oncol Nurs* 2007;**24**:294–8.

Lewden-Bernadac B, Courant-Menanteau M, Perrocheau G, Barbarot V, Thomare P. [Outpatient chemotherapy and oncology network: Onco Pays-de-la-Loire experiment.] *Bull Cancer* 2008;**95**:543–9.

Liston B, Meenaghan T, Wilson H. Home chemotherapy service from University College Hospital Galway. *EJHP Pract* 2009;**15**:45.

Lüthi F, Fucina N, Divorne N, Santos-Eggimann B, Currat-Zweifel C, Rollier P, *et al.* Home care – a safe and attractive alternative to inpatient administration of intensive chemotherapies. *Support Care Cancer* 2012;**20**:575–81.

Midorikawa Y, Suzuki K, Kasuga T, Takemura A. [Our outpatient cases for home anti-cancer chemotherapy.] *Gan To Kagaku Ryoho* 2005;**32**(Suppl. 1):1–3.

Oakley C, Wright E, Ream E. The experiences of patients and nurses with a nurse-led peripherally inserted central venous catheter line service. *Eur J Oncol Nurs* 2000;**4**:207–18.

Ranuzzi M. Home-care in advanced breast cancer: results in 144 patients. *Ann Oncol* 2009;**20**:ii69.

Ranuzzi M, Taddei A, Brunetti S, Gentile S, Vercelloni R, Scarpati S. 10 years experience in home-care with cancer patients. *Support Care Cancer* 2009;**17**:973.

Raphael R, Yves D, Giselle C, Magali M, Odile CM. Cancer treatment at home or in the hospital: what are the costs for French public health insurance? Findings of a comprehensive-cancer centre. *Health Policy* 2005;**72**:141–8.

Richardson J, Townsend C, Holland D. *Outreach Clinics, Ipswich, Anglia Cancer Network. A patient Survey of a Nurse-Led Outreach Service.* URL: www.ukchemotherapypartnership.org.uk/service_models/closer_to_home (retrieved 21 November 2013).

Sato K, Takahashi T, Ashikaga K, Hanyu N, Aoiki T. [Clinical study of home hepatic arterial infusion chemotherapy for liver metastasis from colorectal cancer.] *Gan To Kagaku Ryoho* 1996;**23**(Suppl. 3):252–5.

Sawada K, Sawada M, Suzuki Y, Nakamura M. [Experience of cancer home chemotherapy with cooperation between hospital and clinic.] *Gan To Kagaku Ryoho* 1998;**25**(Suppl. 4):625–30.

Sawada K, Tan M, Kanno M, Saitou K, Oikawa K, Shibuya S, *et al.* [Home chemotherapy for peritoneal carcinomatosis.] *Gan To Kagaku Ryoho* 1994;**21**(Suppl. 4):463–9.

Schlag P, Feil H, Ruoff G, Hohenberger P, Hölting T, Buhl K. [Home treatment of cancer: experiences with ambulatory intra-arterial chemotherapy of liver metastases.] *Schweiz Med Wochenschr* 1987;**117**:1342–6.

Taylor H, Ireland J, Duggan C, Bates I. Home chemotherapy – a feasibility study. *Br J Home Healthcare* 2007;**3**:4–5.

Watty K, White MA, Matthews JP, Buchanan L, Clarke JL, Sulkowski AJ, *et al.* There's no place like home: a prospective evaluation of chemotherapy in the home. *Aus J Cancer Nurs* 2003;**4**:18.

Yamada M, Hasegawa A, Matsuura C, Chen JT. [A study of quality of life for cancer chemotherapy patients: a comparison between hospital treatment and home treatment.] *Kango Kenkyu* 1997;**30**:425–34.

Community studies (single setting)

Bakker DA, DesRochers C, McChesney C, Fitch M, Bennett J. Community cancer clinics: patients' perspectives. *Support Care Cancer* 2001;**9**:234–40.

Gordon J, Gruber M. An innovative off-campus infusion suite designed to improve experiences of patients with cancer. *Clin J Oncol Nurs* 2012;**16**:354–9.

Iredale R, Hilgart J, Hayward J. Patient perceptions of a mobile cancer support unit in South Wales. *Eur J Cancer Care* 2011;**20**:555–60.

Turner C, Pateman B. A study of district nurses' experiences of continuous ambulatory chemotherapy. *Br J Community Nurs* 2000;**5**:396–400.

Outpatient studies (single setting, with qualitative outcomes)

Hjörleifsdóttir E, Hallberg IR, Gunnarsdóttir ED, Bolmsjö IA. Living with cancer and perception of care: Icelandic oncology outpatients, a qualitative study. *Support Care Cancer* 2008;**16**:515–24.

McIlfatrick S, Sullivan K, McKenna H, Parahoo K. Patients' experiences of having chemotherapy in a day hospital setting. *J Adv Nurs* 2007;**59**:264–73.

Appendix 3 Randomised controlled trial study details

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Borras *et al*. 2001,[35] full published paper Linked references: none Design: RCT (parallel group) Country: Spain Recruitment period: October 1997 to October 1998 Number of recruiting centres: one Assessment time points: 'Treatment completion'. This was approximately 6–8 months for palliative patients and 12 months for adjuvant patients	Key characteristics of recruited population: Inclusion criteria: adults (aged 18–75 years) with colorectal cancer were eligible Mean age: 60 years Gender: 45/87 male (52%) Cancer type: colon 40/87 (46%); rectum 27/87 (31%); advanced disease 20/87 (23%) Mean Karnofsky index score: 83 Treatment intention: curative (adjuvant) 70/87 (80%) or palliative 17/87 (20%) Chemotherapy used: fluorouracil	Setting details: home Delivered by a trained nurse (no further details) Hospital (outpatient) Standard care in outpatient clinic (no further details) Preparation of chemotherapy: NR	Target sample size: NR Number actually randomised: 87 Estimated monthly rate of randomisation, per centre: 6.7 Number of eligible participants who were not randomised because of setting preference: NR (only one eligible patient was not randomised) Did it appear that all eligible patients were invited to participate? NR Withdrawals and dropouts 31/87 (36%) patients did not complete chemotherapy 6/42 (14%) outpatients and 1/45 (2%) home patient withdrew voluntarily (no reason details provided) 13/42 (31%) outpatients and 11/45 (24%) home patients withdrew because of toxicity, disease progression or doctor advice	Primary outcome(s): not specified Other outcomes: treatment toxicity (ECOG); withdrawals; use of health-care resources; quality of life (EORTC QOL-C30); satisfaction with health care; Karnofsky Index Qualitative data reported? No Economic data reported? Yes Comments
Main reference: Chen and Hasuimi 1999,[27] conference abstract Linked references: none Design: randomised trial Country: Japan Recruitment period: NR	Key characteristics of recruited population: the only details reported were that patients had been operated on for ovarian cancer Treatment intention: NR Chemotherapy used: all patients received cisplatin 15 mg per square metre (days 1–5), doxorubicin 35 mg per square metre (day 1),	Setting details: home; outpatient Preparation of chemotherapy: NR	Target sample size: NR Number actually randomised: 10 Estimated monthly rate of randomisation: cannot be calculated Number of eligible participants who were not randomised because of setting preference: NR	Primary outcome(s): not specified Other outcomes: quality of life, State Trait Anxiety Inventory, mean nursing time Qualitative data reported? No Economic evaluation: no

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Number of recruiting centres: one Assessment time points: days 1, 3 and 5 of first course of chemotherapy	cyclophosphamide 350 mg per square metre (day 1)		Did it appear that all eligible patients were invited to participate? NR Withdrawals and dropouts: NR	Comments: the study aimed to compare the effect of setting on outcomes following the first course of chemotherapy. One group received the first course at home (followed by outpatient chemotherapy) and the other received the first course in the outpatient setting (followed by home chemotherapy)
Main reference: Christiansen *et al.* 2011,[28] conference abstract Linked references: none Design: RCT (crossover) Country: Denmark Recruitment period: November 2007 to November 2010 Number of recruiting centres: one Assessment time points: Quality of life: at baseline and before each treatment (total of eight treatments including initial outpatient clinic treatment) Preference: at baseline, change of treatment setting, and end of treatment	Key characteristics of recruited population: Inclusion criteria: patients with colon cancer who were eligible to receive adjuvant treatment with oxaliplatin and capecitabine Median age: 64 years Gender: 27/51 (53%) female Treatment intention: curative (adjuvant) Chemotherapy used: oxaliplatin and capecitabine every 3 weeks	Setting details: home Hospital (outpatient): all patients received first infusion at the outpatient clinic before randomisation (for safety reasons) No further details for either setting were reported Preparation of chemotherapy: NR	Target sample size: NR Number actually randomised: 51 Estimated monthly rate of randomisation, per centre: 1.4 Number of eligible participants who were not randomised because of setting preference: NR Did it appear that all eligible patients were invited to participate? NR Withdrawals and dropouts: 14 patients did not complete all eight treatments	Primary outcome(s): not specified Other outcomes: quality of life (EORTC QLQ-C30); adverse effects; time spent receiving chemotherapy; patient preference; costs Qualitative data reported? No Economic evaluation: no Comments

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Corrie *et al.* 2013,[4] full published paper Linked references: protocol;[98] conference posters;[99,100] project report form (Corrie, 2013, Cambridge University Hospitals NHS Foundation Trust, unpublished document) Design: RCT (parallel group) Country: England Recruitment period: January 2009 to May 2011 Number of recruiting centres: two Assessment time points: 4, 8 and 12 weeks. Optional 24-week (or treatment cessation) assessment	Key characteristics of recruited population: Inclusion criteria: adults with an ECOG status of 0–2, scheduled to receive at least 12 weeks of treatment, living within a 30-minute drive of the recruiting hospital, and infusion lasting no more than 4 hours Exclusion criteria: life expectancy under 6 months, participation in a clinical trial (of unlicensed drug) Gender: 33/97 male (34%) Cancer type: breast 36/97 (37%); lung 27/97 (28%); pancreatic 21/97 (22%); other 13/97 (13%) ECOG status: 0 = 65/97 (67%); 1 = 26/97 (27%); 2 = 6/97 (6%) Prior cancer drug: no = 50/97 (52%), yes = 47/97 (48%) Treatment intention: curative (33%), palliative (53%) or supportive care (14%) Chemotherapy used: no details on drugs or regimes used, but delivered based on standard operating procedures	Setting details: Home: chemotherapy delivered by a single nurse in the patient's home GP surgery: offered a choice of three local surgeries all with free parking and conveniently located with respect to the two recruiting hospitals Hospital: outpatient and day unit Preparation of chemotherapy: chemotherapy drugs prepared by oncology pharmacists in the two key hospitals, then dispensed and collected by nurse for delivery in the community	Target sample size: 390 Number actually randomised: 97 Estimated monthly rate of randomisation, per centre: 1.7 Number of eligible participants who were not randomised because of setting preference: 53. 16 patients were reluctant to receive treatment at a GP surgery, two did not want home treatment and 35 wanted to be treated in hospital Did it appear that all eligible patients were invited to participate? The authors indicated that clinicians were somewhat reluctant to refer patients into the trial, citing concerns about patient and nurse safety and resource use. Also see 'Comments' Withdrawals and dropouts: data for 57 patients could be analysed at end of trial. Six patients failed to start treatment, 17 patients did not complete 12 weeks of treatment Home: 33 allocated, 33 started, five stopped, five incomplete data sets GP: 32 allocated, 29 started, eight stopped, four incomplete data sets Hospital: 32 allocated, 29 started, four stopped, right incomplete data sets	Primary outcome(s): patient-reported quality of life, using the Emotional Function domain of the EORTC QLQ-30 questionnaire Other outcomes: EORTC QLQ-C30 (self-rated health); HADS Anxiety; HADS Depression; EQ-5D; costs; satisfaction; serious adverse events Economic evaluation? Yes Type of economic evaluation: CUA Currency (price year): GBP (£) NR Study perspective: not explicitly reported, appears to be NHS perspective Qualitative data reported? Yes Comments: the trial stopped prematurely due to poor accrual rate, on the advice of the independent data monitoring committee Results reported only as differences (between groups)

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Hall and Lloyd 2008,[30] full paper Linked references: none Design: RCT (parallel) Country: UK (England) Recruitment period: 6 months (no dates reported) Number of recruiting centres: one Assessment time points: after the 4th treatment cycle	Key characteristics of recruited population: Inclusion criteria: breast cancer patients intending to receive a minimum of four cycles of anthracycline-based chemotherapy Cancer type: breast cancer No other data regarding patient characteristics were provided Treatment intention: treatment used either to prevent recurrence or metastatic spread in early-stage disease, or for palliation of symptoms in advanced disease cases Chemotherapy used: anthracycline-based chemotherapy	Setting details: Home: no details reported Hospital (outpatient): no details reported Preparation of chemotherapy: NR	Target sample size: 20 Number actually randomised: 15 Estimated monthly rate of randomisation, per centre: 2.5 Number of eligible participants who were not randomised because of setting preference: NR Did it appear that all eligible patients were invited to participate? Patients were identified as being suitable for the study by oncologists or breast cancer nurse specialists at their oncology appointments, and were recruited by the nurse consultant Withdrawals and dropouts: NR	Primary outcome(s): not specified Other outcomes: patient experience and satisfaction; costs Qualitative data reported? Yes Economic data reported? No Comments: primarily a qualitative study
Main reference: King *et al.* 2000,[31] full published paper Linked references: King *et al.* 2001,[54] letters to editor; Caleo *et al.* 1996,[101] conference abstract Design: RCT (crossover) Country: Australia Recruitment period: 1993–5 Number of recruiting centres: two	Key characteristics of recruited population: Inclusion criteria: patients who lived in a ≈ 20 km radius of the respective hospital and whose planned treatment consisted of one of the trial chemotherapy regimens Mean age: NR Gender: NR Cancer type: Early colon cancer: 27/74 (36%) Early-stage breast cancer: 21/74 (28%)	Setting details: Home: treatment provided by existing hospital-based oncology nursing staff. Nurses travelled from the medical oncology unit closest to the patient's home Hospital (outpatient): no details provided Preparation of chemotherapy: NR	Target sample size: NR Number actually randomised: 74 Estimated monthly rate of randomisation, per centre: 1.5 Number of eligible participants who were not randomised because of setting preference: 13. Four patients felt safer in hospital; two thought that their home was unsuitable owing to social problems; one did not want to associate home with chemotherapy; and six thought that being in the study would be more inconvenient than regular hospital care	Primary outcome(s): not specified Other outcomes: patient and carer preferences and strength of preference; patient and carer satisfaction; unmet patient needs; patient quality of life (FLIC); costs Qualitative data reported? No Economic evaluation? Yes Type of economic evaluation: CEA Currency (price year): AUD ($) NR Study perspective: health service Comments: one ineligible patient was

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Assessment time points: Patient quality of life: recruitment to study and at each chemotherapy treatment session Preference and satisfaction: after 2 and 4 months (end of setting periods) Unmet needs: NR	Metastatic breast cancer: 25/74 (34%) Head and neck cancer: 1/74 (1%) Treatment intention: adjuvant (colon and early breast cancer, 65%) or palliative (metastatic breast cancer, 34%); NR for head and neck cancer Chemotherapy used: 5-flourouracil and levamisole (colon cancer); intravenous CMF, methotrexate and 5-fluorouracil (CMF; early breast cancer); oral CMF (metastatic breast cancer); and methotrexate (head and neck cancer)		Did it appear that all eligible patients were invited to participate? Patient recruitment to the trial was dependent on the medical oncologist or oncologist nurses' judgement of the patient's applicability to the trial Withdrawals and dropouts: 34 (46%) patients did not complete both home and hospital treatments. Eight patients revoked consent to home treatment after receiving hospital treatment in the run-in period. Four patients developed conditions (mostly poor venous access) which meant that chemotherapy was technically too difficult to administer at home. Two patients moved residence outside the treatment zone	recruited at a time when participation rates were low
Main reference: Pace *et al.* 2009,[29] full published paper Linked references: Pace *et al.* 2007[102] Design: RCT (crossover) Country: UK (England) Recruitment period: August 2005 to August 2006	Key characteristics of recruited population: Inclusion criteria: patients ≥ 18 years without previous chemotherapy treatment, scheduled to receive standard chemotherapy for at least six cycles suitable for day-case administration, without other uncontrolled medical illness. WHO status of 0, 1, 2 Median age: 57 years (range 40–80 years)	Setting details: Community (OUTREACH centre): four centres none previously having delivered chemotherapy. Facilities included a waiting area, emergency call facilities and resuscitation equipment. Only chemotherapy was delivered during sessions in these areas Located 6, 13, 20 and 25 miles from the cancer centre	Target sample size: 30 Number actually randomised: 42 Estimated monthly rate of randomisation, per centre: 3.2 Number of eligible participants who were not randomised because of setting preference: five, all female, reasons relating to safety concerns or convenience	Primary outcome(s): patient preference for location of treatment (measured via questionnaire) Other outcomes: HADS; C-SAS (toxicity scale); CPSQ (patient satisfaction questionnaire); resource use; safety Qualitative data reported? Yes Economic data reported? Yes

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Number of recruiting centres: one Assessment time points: Based on cycles: 1, 3, 4, 5 and completion for most outcomes, toxicity measured at each cycle	Gender: male 7/42 (17%); female 35/42 (83%) Disease stage: early 29/42 (69%); advanced 13/42 (31%) Cancer type: breast 32/42 (76%); pancreas 2/42 (5%); prostate 2/42 (5%); melanoma 2/42 (5%); other 4/42 (9%) Treatment intention: 'standard chemotherapy'; no further details given Chemotherapy used: anthracycline-based regimes 31/42 (74%) gemcitabine; carboplatin-based regimes; docetaxel; dacarbazine; COIN study treatment	Hospital outpatient: dedicated chemotherapy suite within an oncology unit, including dedicated patient support and information centre. All chemotherapy was delivered by members of the hospital chemotherapy team both in the cancer centre and within the community settings Preparation of chemotherapy: chemotherapy was made to prescription for individual patients and delivered to the oncology day unit. From there it was collected and then taken to the community hospital by a member of the team	Did it appear that all eligible patients were invited to participate? Participants were recruited from a consecutive series, estimated 98 were eligible, most reasons for non-entry were unknown Withdrawals and dropouts: 38 (90.5%) completed the first two cycles of chemotherapy at the first location; 31 (73.8%) completed the first four cycles of chemotherapy and therefore crossed over from one location to the second; and 28 (66.7%) completed six cycles of chemotherapy Reasons for withdrawal: disease progression and cessation of chemotherapy	Type of economic evaluation: CEA Currency (price year): GBP £ NR Economic perspective: NHS and patient (not explicitly reported) Comments: authors comment that the preference for the outreach location was not mirrored in global CPSQ and HADS scores. They suggest that the CPSQ and HADS may be missing aspects of the chemotherapy experience that people consider important, and determine their treatment location preferences Project was not pursued further due to lack of funding; however, a local patient-led initiative has established a charity and funds the OUTREACH project. See www.chemooutreachproject.co.uk for more details

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Remonnay *et al.* 2002,[34] full paper Linked references: Remonnay *et al.* 2003,[103] full published paper (French) Design: RCT (crossover) Country: France Recruitment period: October 1995 to June 1998 Number of recruiting centres: one Assessment time points: patients were assessed after two courses of chemotherapy, switched from home to hospital or vice versa, and then were assessed after two further courses of chemotherapy	Key characteristics of recruited population: All patients had previously been hospitalised at the recruiting centre Inclusion criteria: the patient must have not received chemotherapy in the previous 2 months, the patient lived in the geographical area covered by Soins et Santè, the patient lived with a family member, the patient's personal physician consented, and the patient had permanent access to a vein or an implantable venous access system (Port-A-Cath) Mean age: 60 years (SD 11 years) Gender: 17% male Type of cancer: mostly breast cancer (81%). Some patients had non-small cell lung cancer Treatment intention: unclear Chemotherapy used: most frequently used chemotherapy regimens were cyclophosphamide and doxorubicin, cyclophosphamide, methotrexate, and 5-fluorouracil and navelbine	Setting details: Home: no details reported Outpatient: no details reported Preparation of chemotherapy: it was unclear where the chemotherapy was prepared, but costs for drugs were higher for home care due to not being provided by the hospital	Target sample size: 160 Number actually randomised: 52 Estimated monthly rate of randomisation, per centre: 1.6 Number of eligible participants who were not randomised because of setting preference: 10 participants; six refused due to lack of confidence in home delivery and four due to not wanting to impose on loved ones Did it appear that all eligible patients were invited to participate? NR Withdrawals and dropouts: 10 dropouts; six died and four reported deterioration requiring change of treatment	Primary outcome(s): patient satisfaction Other outcomes: costs, quality of life (FLIC, MADRS), Hamilton Anxiety Scale Quality of life and anxiety results NR, no response to author contact Qualitative data reported? No Economic evaluation? Yes Type of economic evaluation: CEA Currency (price year): US$ (1998) converted using purchasing power parities Economic perspective: societal Comments: care administered by external organisation Soins et Santé. Trial was terminated early because 95% of the first 52 patients expressed a preference for home administration of chemotherapy. The authors assumed that there were no costs for administration in the outpatient setting. Of outcomes listed for the trial, only costs were reported in this study

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Rischin *et al.* 2000,[32] full published paper Linked references: King *et al.* 2001,[54] letters to editor Design: RCT (crossover) Country: Australia Recruitment period: February 1996 to March 1997 Number of recruiting centres: one Assessment time points: after one treatment in each setting	Key characteristics of recruited population: Inclusion criteria: patients aged ≥ 18 years, who had not received chemotherapy in the preceding 12 months, whose planned first two treatments were identical, and who lived in an area that was geographically suitable for treatment at home Median age: around 60 years Gender: 5/20 (25%) male Cancer type: breast 10/20 (50%); colon 8/20 (40%); non-Hodgkin's lymphoma 1/20 (5%); pancreatic 1/20 (5%) Treatment intention: NR Chemotherapy used: cyclophosphamide, methotrexate and 5-fluorouracil ± prednisolone [CMF(P)] 50%; 5-FU ± folinic acid or levamisole 45%; cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) 5%	Setting details: Home: a chemotherapy nurse specialists who also worked in the chemotherapy day ward at the hospital administered all home chemotherapy treatments Hospital (outpatient): chemotherapy administered by hospital chemotherapy nurse specialist. No further details reported Preparation of chemotherapy: NR	Target sample size: 20 Number actually randomised: 25 Estimated monthly rate of randomisation: 1.8 Number of eligible participants who were not randomised because of setting preference: seven patients wanted home treatment only and 12 were 'overlooked' Did it appear that all eligible patients were invited to participate? No: 12 patients were overlooked in the recruitment stage (no further details were provided). In addition, patients were selected from patients registered on the chemotherapy-in-the-home program, for which eligibility criteria were NR Withdrawals and dropouts: in the 'hospital first' arm three patients withdrew – one patient did not go on to receive chemotherapy, one received chemotherapy at home and one decided to have all chemotherapy in hospital after the first treatment In the 'home first' arm, two patients withdrew: one person did not go on to receive any chemotherapy, and one patient had a change of chemotherapy regimen due to toxicity after cycle 1	Primary outcome(s): patient preferred site for remaining treatments Other outcomes: patient preference; patient satisfaction; complications; costs Qualitative data reported? Yes Economic evaluation? Yes Type of economic evaluation: CEA Currency (price year): AU$ NR Study perspective: hospital Comments: all eligible patients were 'registered on the chemotherapy in the home program'. It appears that home chemotherapy was already an option outside of the trial setting. The targeted trial population seems to exclude those patients more likely to prefer the hospital setting Only one treatment per setting was studied

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Stevens *et al.* 2006,[33] full published paper Linked references: full published paper Stevens *et al.* 2006;[55] full published paper Stevens *et al.* 2004;[56] editorial[104] Design: RCT (crossover) Country: Canada Recruitment period: NR Number of recruiting centres: one Assessment time points: baseline, 3 months, 6 months (prior to crossover) and then at 9 months (first assessment after crossover) and 12 months	Key characteristics of recruited population: Inclusion criteria: children age 2–16 years of age, diagnosed with acute lymphoblastic leukaemia, being treated by standard protocol in the greater metropolitan area of the study Exclusion criteria: children with other major congenital illnesses and those who did not have a patent central venous catheter Age: NR Gender: male 22/29 (75.9%) Phase of chemotherapy: III 1/29 (3.4%) interim maintenance; IV 4/29 (13.8%) reinduction; V 24/29 (82.8%) maintenance Treatment intention: curative Chemotherapy used: intrathecal methotrexate, intravenous cyclophosphamide, vincristine, intravenous methotrexate, cytosine arabinoside (Ara C)	Setting details: Home: some chemotherapy drugs were delivered in hospital for safety reasons; these included intrathecal methotrexate, intravenous cyclophosphamide, and vincristine. These drugs were delivered by standard protocol. Intravenous methotrexate and Ara C were delivered in patients' homes by a trained community health services agency nurse. Blood samples were taken at a community laboratory the day prior to administration of chemotherapy. The primary oncology nurse was the main support nurse Hospital (outpatient): patients received chemotherapy by standard hospital protocol. Blood samples were taken during scheduled visits Preparation of chemotherapy: home – chemotherapy drugs were prepared by a community pharmacy and delivered to patients' homes at pre-arranged times	Target sample size: 22 Number actually randomised: 29 Estimated monthly rate of randomisation: not possible to calculate Number of eligible participants who were not randomised because of setting preference: 21 eligible patients declined to participate; 16 preferred hospital treatment; three preferred to keep home as a safe haven; two provided no reason Did it appear that all eligible patients were invited to participate? Yes Withdrawals and dropouts: Home followed by hospital chemotherapy: two discontinued (relapse) Hospital followed by home chemotherapy: four discontinued (two withdrew, two relapse). No reason was given for withdrawals	Primary outcome(s): patient quality of life was measured using the POQOLS questionnaire, and the Child Behaviour Checklist was used to measure social/psychological interactions of children Other outcomes: caregiver burden as measured with the Caregiving Burden Scale; adverse events; costs Qualitative data reported? Yes Economic evaluation: yes Economic evaluation type: CEA Currency (price year): $CAN NR Economic perspective: societal Comments

CEA, cost-effectiveness analysis; CMF, cyclophosphamide; COIN, COntinuous chemotherapy plus cetuximab or INtermittent chemotherapy with standard continuous combination chemotherapy; CPSQ, Chemotherapy Patient Satisfaction Questionnaire; C-SAS, Chemotherapy Symptom Assessment Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; NR, not reported; WHO, World Health Organization.

Appendix 4 Randomised controlled trial risk of bias

Type of bias	Judgement (high, low or unclear risk)	Support for judgement
***Borras* et al. *2001*[35]**		
Random sequence generation	Low	Random numbers were selected in blocks of eight, stratified according to type of tumour
Allocation concealment	Unclear	Does not report who performed the randomisation or any details of concealment process
Similarity at baseline	Low	Groups very similar for gender, age, tumour site, toxicity, treatment type or radiotherapy use
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes subjective (patients not blinded)
	Low	Adverse events/toxicity unlikely to be affected
	Low	Use of health-care resources (unplanned hospitalisation, or primary care or emergency department visits) unlikely to be affected
Incomplete outcome data	Unclear	6/42 (14%) outpatients and 1/45 (2%) home patient withdrew voluntarily. This difference was statistically significant. However, no details were provided
Selective reporting	Low	Could not locate trial protocol, although it appears from the paper that all collected outcomes were reported (and in sufficient detail)
Other bias (crossover trials only): N/A		
***Chen and Hasuimi 1999*[27]**		
Random sequence generation	Unclear	'Random'
Allocation concealment	Unclear	Study reported as a brief conference abstract
Similarity at baseline	Unclear	Study reported as a brief conference abstract
Blinding of participants and researchers	Unclear	Study reported as a brief conference abstract
Blinding of outcome assessment	Unclear	Study reported as a brief conference abstract
Incomplete outcome data	Unclear	Study reported as a brief conference abstract
Selective reporting	High	No actual data reported for quality-of-life (and related) outcomes
Other bias (crossover trials only):		
Crossover a suitable design? N/A		
Appropriate statistical analysis used (to allow for pairing)? N/A		

Type of bias	Judgement (high, low or unclear risk)	Support for judgement
***Christiansen* et al. *2011*[28]**		
Random sequence generation	Unclear	'Randomised' only details given
Allocation concealment	Unclear	Not reported
Similarity at baseline	Low	Crossover trial: within participant comparisons
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes subjective (patients not blinded)
Incomplete outcome data	Unclear	14 patients did not complete treatment, no further details reported
Selective reporting	Unclear	Protocol not available, and unclear from abstract whether or not other outcomes were assessed
Other bias (crossover trials only):		
Crossover a suitable design? Unclear – abstract only available		
Appropriate statistical analysis used (to allow for pairing)? Unclear – abstract only available		
***Corrie* et al. *2013*[4]**		
Random sequence generation	Low	Randomised by independent centre using minimisation
Allocation concealment	Low	Central allocation – participants were allocated a unique trial number and the treatment setting defined. The randomisation outcome information was provided to the investigator within 24 hours
Similarity at baseline	Low	Well balanced in terms of key characteristics due to use of minimisation
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes and service use data, for example family care and travel time (patients not blinded)
	Low	Adverse events unlikely to be affected
	Low	
Incomplete outcome data	Low	Data for 57 patients could be analysed at end of trial. Six patients failed to start treatment, 17 patients did not complete 12 weeks of treatment
		Home: 33 allocated, 33 started, five stopped, five incomplete data sets
		GP: 32 allocated, 29 started, eight stopped, four incomplete data sets
		Hospital: 32 allocated, 29 started, four stopped, eight incomplete data sets
Selective reporting	Low	Protocol available and checked
Other bias (crossover trials only): not relevant		

Type of bias	Judgement (high, low or unclear risk)	Support for judgement
Hall and Lloyd 2008[30]		
Random sequence generation	Unclear	'Randomly allocating' patients
Allocation concealment	Unclear	No details reported
Similarity at baseline	Unclear	No details reported
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes subjective (patients not blinded)
Incomplete outcome data	Unclear	Appear to have full follow-up data (although not explicitly stated)
Selective reporting	Unclear	Could not locate trial protocol, appears from the paper that all collected outcomes were reported
Other bias (crossover trials only): N/A		
King* et al. *2000[31]		
Random sequence generation	Low	Random number table, stratified by cancer type
Allocation concealment	Unclear	Mentions use of sealed envelopes but not whether they were opaque or sequentially numbered
Similarity at baseline	Low	Crossover trial: within-participant comparisons
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes subjective (patients not blinded)
Incomplete outcome data	Low	Eight participants withdrew from receiving home treatment after experiencing outpatient treatment. However, additional analyses were conducted which assumed such patients preferred outpatient treatment
Selective reporting	Unclear	Protocol not available
Other bias (crossover trials only):		
Crossover a suitable design? Overall, yes, although seven patients dropped out because of disease progression (using only the early breast cancer population may have been preferable)		
Appropriate statistical analysis used (to allow for pairing)? Yes, used paired analyses and checked for period effects (data from both periods were used), interactions and carryover effects		

Type of bias	Judgement (high, low or unclear risk)	Support for judgement
***Pace* et al. *2009*[29]**		
Random sequence generation	Unclear	'Telephone randomisation, in blocks of 10, to local Research Support Unit', but unclear exactly how sequence was generated
Allocation concealment	Low	Although this is assuming the blocks of 10 were used only by the local research support unit and not by the investigators
Similarity at baseline	Low	Crossover trial: within-participant comparisons
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes subjective (patients not blinded)
Incomplete outcome data	Unclear	43% attrition throughout the study due to disease progression and cessation of chemotherapy, all outcomes reported for completing patients. Attrition not reported by treatment location so difficult to assess if differential loss of data
Selective reporting	Low	Could not locate trial protocol, but appears from the paper that all collected outcomes were reported
Other bias (crossover trials only):		
Crossover a suitable design? Probably not – too many patients withdrew due to disease progression and cessation of chemotherapy		
Appropriate statistical analysis used (to allow for pairing)? Unclear, although data from both time periods were used		
***Remonnay* et al. *2002*[34]**		
Random sequence generation	Unclear	'Order of passage was selected at random' only reported in English paper
Allocation concealment	Unclear	Not reported
Similarity at baseline	Low	Crossover trial: within-participant comparisons
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	Unclear	Not reported
Incomplete outcome data	Unclear	No numerical data (only a percentage) reported for preference data
Selective reporting	High	No protocol available; only economic data reported although quality of life also measured
Other bias (crossover trials only):		
Crossover a suitable design? No – six patients died and four reported deterioration requiring change of treatment (total $n = 52$)		
Appropriate statistical analysis used (to allow for pairing)? Details not reported		

Type of bias	Judgement (high, low or unclear risk)	Support for judgement
***Rischin* et al. *2000*[32]**		
Random sequence generation	Low	Computer-generated randomisation chart using an allocation scheme based on a biased coin design
Allocation concealment	Unclear	Not described, mention of a chart suggests may not have been concealed
Similarity at baseline	Low	Crossover trial: within-participant comparisons
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes subjective (patients not blinded)
	Low	Serious adverse events unlikely to be affected
Incomplete outcome data	Low	Three withdrawals in hospital first arm, and two in home first arm with reasons given
Selective reporting	Unclear	Protocol not available, and unclear from paper whether or not other outcomes were assessed
Other bias (crossover trials only):		
Crossover a suitable design? Yes, no withdrawals due to disease progression		
Appropriate statistical analysis used (to allow for pairing)? Yes, used paired analyses using data from both time periods, and checked for period and carryover effects		
***Stevens* et al. *2006*[33]**		
Random sequence generation	Low	Table of random numbers
Allocation concealment	Unclear	Allocation performed by study site manager but unclear if group identity was concealed
Similarity at baseline	Low	Crossover trial: within-participant comparisons
Blinding of participants and researchers	High	Neither participants nor researchers were blinded
Blinding of outcome assessment	High	Patient-reported outcomes subjective (patients not blinded)
	Low	Adverse events unlikely to be affected
Incomplete outcome data	Low	23/29 children completed both phases and appear to have recorded all outcome data; relapse similar in both arms but reasons for withdrawal ($n = 2$) not reported
Selective reporting	Low	Could not locate trial protocol; appears from the paper that all collected outcomes were reported
Other bias (crossover trials only):		
Crossover a suitable design? Appears reasonable, disease course relatively stable		
Appropriate statistical analysis used (to allow for pairing)? Paired analyses (data from both periods) were used and checked for period and programme effects or interactions		

N/A, not applicable.

Appendix 5 Results

Results for quality-of-life outcomes

Study	Outcomes
Randomised trials	
Corrie *et al.* 2013[4]	*EORTC QLQ-C30 self-rated QoL*
	Community ($n = 39$) vs. outpatient ($n = 17$): –0.01 (95% CI –0.87 to 0.86; $p = 0.99$)
	Home ($n = 23$) vs. GP ($n = 16$): –0.06 (95% CI –0.99 to 0.88; $p = 0.90$)
	Home ($n = 23$) vs. outpatient ($n = 17$): –0.03 (95% CI –0.99 to 0.93; $p = 0.95$)
	GP ($n = 16$) vs. outpatient ($n = 17$): 0.03 (95% CI –0.99 to 1.05; $p = 0.96$)
	EORTC QLQ-C30 Emotional Function domain
	Community (home and GP, $n = 38$) vs. outpatient ($n = 17$): –7.2 (95% CI –19.5 to 5.2; $p = 0.25$)
	Home ($n = 23$) vs. GP ($n = 15$): 15.2 (95% CI 1.3 to 29.1; $p = 0.033$)
	Home ($n = 23$) vs. outpatient ($n = 17$): –1.5 (95% CI –14.5 to 11.5; $p = 0.82$)
	GP ($n = 15$) vs. outpatient ($n = 17$): –16.6 (95% CI –31.4 to –1.9; $p = 0.028$)
	EQ-5D
	Utility scores: not reported
	QALYs
	Home: 0.174 (SD 0.034)
	Community (GP): 0.191 (SD 0.040)
	Hospital: 0.165 (SD 0.053)
Borras *et al.* 2001[35]	*EORTC QLQ-C30 self-rated QoL*
	Home ($n = 33$): 71 (SD 17); outpatient ($n = 23$): 68 (SD 20); 'no difference', nor in changes from baseline
	EORTC QLQ-C30 Emotional Function domain
	Home ($n = 33$): 76 (SD 24); outpatient ($n = 23$): 79 (SD 19); 'no difference', nor in changes from baseline
	EORTC QLQ-C30
	Results were also presented for the individual items of the functional and symptom domains of EORTC QOL-C30
King *et al.* 2000[31]	*FLIC (self-administered questionnaire)*
	Overall total FLIC score: 76 (SD 14, interaction $p = 0.23$). Setting-specific scores were not reported. The 'location effect' was –0.49 ($p = 0.79$), i.e. treatment location (home or hospital) did not have a significant impact on quality of life
	Note: 'period effects' also reported
	FLIC Emotional Function subscore: overall average score of 72 (SD= 19, interaction $p = 0.30$). The location effect was –0.09 ($p = 0.98$)
	Note: other FLIC subscores were also recorded (role function, pain, hardship, current health, sociability and nausea)

Study	Outcomes
Christiansen *et al.* 2011[28]	*EORTC QLQ-C30 self-rated QoL* There was no significant difference between hospital-treated and home-treated patients' QoL scores. No raw results were reported
Stevens *et al.* 2006[33]	*POQOLS; Child Behaviour Checklist* POQOLS Factor 1 (sensitivity to restrictions in physical functioning and the ability to maintain a normal physical routine): Crossover to outpatient led to a 5.2 increase ($n = 13$ before switch, $n = 13$ after, lower is better). Crossover to home led to a 10.5 decrease ($n = 14$ before switch, $n = 10$ after). The difference between the two groups was significant ($p = 0.023$). There were 13 patients with baseline measurements in the home group, with a maximum of 14 observations at any follow-up period, and 12 at the final follow-up. For the hospital group, there were 14 patients at baseline, and 10 at final follow-up Factor 2 (emotional distress): No significant difference due to crossover. Patients starting at home had statistically significantly higher scores (lower QoL) at 6 months than those starting in outpatient setting (6.8 difference, $p = 0.043$) Factor 3 (reaction/response to current medical treatment) Non-statistically significantly higher scores in home group (8.3 difference, $p = 0.61$) Long-term trends appeared to indicate little difference between treatment locations in any POQOLS factor
Remonnay *et al.* 2002[34]	*FLIC (self-administered questionnaire)* Results not reported
Chen and Hasuimi 1999[27]	*Unclear QoL measures* The authors stated that, by day 5 of the first course, quality-of-life items (such as mood, smell, appetite and satisfaction) were 'significantly decelerated' in the home-first group compared with the hospital-first group, but no data were reported Intergroup analysis in the hospital first group indicated that the second infusion at home significantly improved QoL status in appetite, taste, mood and satisfaction
Non-randomised studies	
Hansson *et al.* 2013[38]	PedsQL Scale Generic Core Child self-reported and parent proxy (0–100 scale); PedsQL Cancer Module child self-reported and parent proxy (seven dimensions, 0–100 scale); PedsQL Family Impact Module (eight dimensions) *PedsQL Generic Core: child self-reported* Home care $n = 13$; hospital $n = 26$ at T1 (recruitment), $n = 25$ at T2 (3 months). At T1 and T2 all home-care group results were higher than standard care. At T2 self-reported mean scores were statistically significantly higher in the home-care group vs. outpatient in the dimensions of total score (75.3 vs. 61.1; $p = 0.02$), psychosocial health (74.6 vs. 62.4; $p = 0.03$) and emotional functioning (78.1 vs. 62.2; $p = 0.04$). The crude mean difference between settings in global total score between T1 and T2 was 14.2 (95% CI 2.0 to 26.3; $p = 0.02$). The adjusted mean difference was 14.8 (95% CI –0.4 to 30.1; $p = 0.06$). Subscores across time points were reported (see paper). The only dimension statistically significant for the adjusted mean difference value was social functioning: mean difference = 15.5 (95% CI 0.0 to 31.1; $p = 0.05$) (Variables adjusted for age, diagnosis, gender and time since diagnosis) Several children did not attend school, which affects the mean score in the school dimension

Study	Outcomes
	PedsQL Generic Core: parent proxy Home care T1 $n = 40$, T2 = 41; outpatient T1 $n = 62$, T2 $n = 66$. All home scores were higher than outpatient care scores at both time points. The crude mean difference for total score between settings was 7.7 (95% CI 0.4 to 14.9; $p = 0.04$). The adjusted mean difference was 7.7 (95% CI 0.6 to 16.1; $p = 0.07$). For the adjusted scores, only the physical health score was significant: mean difference = 14.2 (95% CI 3.3 to 25.2; $p = 0.01$) (full domain scores reported in paper) *Cancer Module: child self-reported* There were no statistically significant differences between the home-care group and outpatient group across any of the items *Cancer Module: parent proxy* For the adjusted results there were two statistically significant domains: nausea (mean difference = 9.9 (95% CI –0.2 to 19.5; $p = 0.04$) and worry (mean difference = 10.5 (95% CI –0.4 to 20.6; $p = 0.04$) (higher scores are better, scores favoured home setting). Full domain scores in paper *Family Impact Module* The mean scores were similar overall between groups (no result detail reported)
Payne 1992[46]	Domains of a bespoke quality of life implement developed for the study (not detailed elsewhere) All results reported as (mean; SD). HADS Anxiety and Depression form the Psychological Stress domain (see psychological results table). The number of patients for each component was not reported Only gastrointestinal complaints ($p < 0.01$) and housework ($p = 0.01$) had statistically significant differences Physical complaints: • Home – tiredness (4; 2.5), gastrointestinal (2.6; 3.0), pain (1.8; 1.5) • Outpatient – tiredness (5.1; 2.4), gastrointestinal (11.3; 4.2), pain (1.3; 1.6) Marital: • Home – satisfaction (5.3; 2.1) vs. outpatient – satisfaction (6.2; 2.1) Activity: • Home – housework (7.0; 2.0), Karnofsky Performance Scale (45.7; 5.3), plans for the future (6.7; 1.7), self-esteem (72.0; 8.4) • Outpatient – housework (5.8; 1.2), Karnofsky Performance Scale (41.9; 9.4), plans for the future (6.2; 1.8), self-esteem (69.6; 8.4) Regression analyses were conducted to find influential variables. Anxiety accounted for 82% of variance and depression accounted for 10%
Souadjian *et al.* 1992[48]	*Activities of Daily Life* Home patients reported an improvement in quality of life after compared with outpatient chemotherapy. Data were not reported, nor was the method of measurement

QoL, quality of life; T1, time point 1; T2, time point 2.

Results for clinical outcomes

Study	Outcomes
Randomised trials	
Corrie *et al.* 2013[4]	*EORTC QLQ-C30 self-rated health* Community ($n = 39$) vs. outpatient: 0.30 (95% CI –0.51 to 1.12; $p = 0.46$) Home ($n = 23$) vs. GP ($n = 16$): –0.07 (95% CI –0.97 to 0.83; $p = 0.88$) Home ($n = 23$) vs. outpatient ($n = 17$): 0.28 (95% CI –0.62 to 1.17; $p = 0.54$) GP ($n = 16$) vs. outpatient: ($n = 17$) 0.34 (95% CI –0.64 to 1.33; $p = 0.49$)
Borras *et al.* 2001[35]	*EORTC QLQ-C30 self-rated health* Home ($n = 33$) 71 (SD 17) vs. outpatient ($n = 23$) 68 (SD 20). Difference not significant *Karnofsky Index* Home ($n = 33$) 85 (SD 11) vs. outpatient ($n = 23$) 85 (SD 11)
Stevens *et al.* 2006[33]	*Caregiving Burden Scale* No evidence of effect from location
Non-randomised studies	
Payne 1992[46]	*Karnofsky Performance Scale* Home: 45.7 (SD 5.3) vs. outpatient: 41.9 (SD 9.4) ($p = 0.19$)
Pong *et al.* 2000[37]	*Self-rated health status, seven-category Likert sale – survey posted questionnaire* Categories 2 and 3, and 5 and 6 were combined Community (COCN) patients ($n = 153$): • 1 (bad): 1.3% • 2/3: 9.2% • 4 (average): 24.2% • 5/6: 43.8% • 7 (good): 20.9% Hospital patients (NEORCC) ($n = 225$): • 1: 0% • 2/3: 15.8% • 4: 22.8% • 5/6: 46.5% • 7: 15.8% The differences were not statistically significant NB: the hospital sample included both patients who could have taken part in the community ($n = 55$) programme and those who could not

COCN, Community Oncology Clinic Network; NEORCC, Northeastern Ontario Regional Cancer Centre.

Results for psychological outcomes

Study	Outcomes
Randomised trials	
Corrie *et al.* 2013[4]	*HADS Anxiety community* (n = *40) vs. outpatient* (n = *17)*
	0.97 (95% CI –0.97 to 2.9; $p = 0.32$)
	Home ($n = 23$) vs. GP ($n = 17$): –1.97 (95% CI –4.10 to 0.17; $p = 0.07$)
	Home ($n = 23$) vs. outpatient ($n = 23$): 0.13 (95% CI –1.97 to 2.23; $p = 0.90$)
	GP ($n = 23$) vs. outpatient ($n = 17$): 2.10 (95% CI –0.16 to 4.35; $p = 0.07$)
	HADS Depression community (n = *40) vs. outpatient* (n = *17):*
	2.10 (95% CI –0.02 to 4.22; $p = 0.05$)
	Home ($n = 23$) vs. GP ($n = 17$): –2.01 (95% CI –4.31 to 0.27; $p = 0.08$)
	Home ($n = 23$) vs. outpatient ($n = 23$): 1.28 (95% CI –1.00 to 3.55; $p = 0.27$)
	GP ($n = 23$) vs. outpatient ($n = 17$): 3.29 (95% CI 0.81 to 5.77; $p = 0.01$)
Pace *et al.* 2009[29]	*HADS Anxiety*
	No raw data reported; text states no significant difference between arms although tendency for anxiety to decrease over time in both groups
	HADS Depression
	No raw data reported; text states no significant difference between arms although both groups reported rise in depression mid-way in trial; final depression scores lower than mean baseline scores
Stevens *et al.* 2006[33]	*Child Behaviour Checklist*
	No significant differences between treatment groups at any follow-up point
Remonnay *et al.* 2002[34]	*Hamilton Anxiety Scale*
	Results not reported
	Montgomery–Åsberg Depression Rating Scale (MADRS)
	Results not reported
Payne 1992[46]	*HADS Anxiety*
	Home 35.6 (SD = 22) vs. outpatient 44.2 (SD = 32.2) ($p = 0.42$)
	HADS Depression
	Home 28.7 (SD = 20) vs. outpatient 33.5 (SD = 18.3) ($p = 0.51$)
Non-randomised studies	
Herth 1989[43]	*Herth Hope Scale (score range 0–32)*
	Jalowiec Coping Scale (score range 90–200)
	Outpatients had significantly higher levels of coping response and hope
	Hope: home ($n = 20$) 24.1 vs. outpatient ($n = 20$) 27.0 ($p < 0.01$)
	Coping: home ($n = 20$) 121.9 vs. outpatient ($n = 20$) 140.2 ($p < 0.01$)

Results for satisfaction outcomes

Study	Outcomes
Randomised trials	
Corrie *et al.* 2013[4]	*Questionnaire* 78% of patients expressed satisfaction with their treatment setting, whatever their location
Borras *et al*. 2001[35]	*Questionnaire (score range 1–100, larger scores equate to greater satisfaction)* There were significant differences between groups in: • Perceptions of nursing availability [home 87 (SD 7) vs. outpatient 54 (SD 16)] • Communication with nurse [home 100 (SD 0) vs. outpatient 82 (SD 25)] • Personal qualities of nursing [home 98 (SD 6) vs. outpatient 84 (SD 15)] Health care in general was borderline significant [home 86 (SD 13) vs. outpatient 78 (SD 19)]; difference in means –8 (95% CI –17 to 0) There were no significant differences reported for the remaining three types of care (availability of doctor, continuity of care and communication with doctor). Home $n = 33$ and outpatient $n = 23$ (for all)
Hall and Lloyd 2008[30]	*Individual semistructured interviews* See qualitative data extraction
King *et al.* 2000[31]	*Questionnaire (interview) on patient satisfaction* The only statistically significant (setting-related) difference in satisfaction with home vs. outpatient care related to the depressing nature of the place of treatment: 15/40 patients found hospital, but not home, a depressing treatment option; one patient found home, but not hospital, depressing; 24 patients found both depressing. The location effect on this item was –1.23; $p = 0.00$ A significant period effect was found: patients felt significantly less secure during period 2, regardless of setting ($p = 0.04$) *Questionnaire (interview) on patient perception of unmet need* There were no statistically significant location effects on the five patient needs dimensions for the 34 patients who completed the questionnaire *Self-administered questionnaire (carers)* There were no statistically significant location effects on the carer satisfaction scores
Pace *et al.* 2009[29]	*Chemotherapy Patient Satisfaction Questionnaire (CPSQ)* Seven dimensions, each item scored from 1–5, low scores = greater satisfaction Patients were significantly more satisfied with the outreach location for ease of access and environment ($p < 0.001$), and there was greater satisfaction with the outreach centre for interpersonal and technical aspects of nursing care ($p < 0.01$) There were no significant differences in anxiety and global satisfaction More complete data in full paper for each dimension

Study	Outcomes
Rischin *et al.* 2000[32]	*Questionnaire (patients)* None of the patients reported concerns with chemotherapy being given in their home; 4/20 (20%) reported concerns with treatment in hospital, relating to transport difficulties and waiting times (no raw data given) 18/20 (90%) of patients felt there were advantages with treatment in the home. The reasons given included convenience; avoidance of travel and parking problems (particularly not having to travel while feeling unwell); reduction in treatment-associated anxiety; not burdening their carers and family; and being able to continue their duties such as caring for their dependents. One (5%) patient thought that there were specific advantages to chemotherapy in the hospital: being able to see other people who were worse off
Stevens *et al.* 2006[55]	*Qualitative patient satisfaction interviews* See qualitative data extraction
Non-randomised studies	
Grusenmeyer *et al.* 1996[42]	*0–100-mm visual analogue scale (VAS)* Outpatient satisfaction was 98 mm on the VAS; home satisfaction was not reported
Lowenthal *et al.* 1996[45]	*Number of patients choosing to discontinue home treatment* 2 of 424 patients
Barker 2006[40]	*Participant comments to the author* See qualitative results
Pong *et al.* 2000[37]	*Questionnaire: posted survey (7-point sale: 7 = strongly agree, 4 = neutral, 1 = strongly disagree)* Patient satisfaction: Community patients ($n = 153$) were asked a series of questions about patient satisfaction and acceptance of the community programme. Hospital patients ($n = 114$) were asked similar questions in order to provide a basis for comparison Generally satisfaction was high About half of those who had received their first chemotherapy treatment at hospital said that the treatment skills and knowledge of those at hospital were superior to those at the community clinics. Hospital patients tended to have more access to sources of information, but did not necessarily use these sources more frequently than community patients. About 85% of the hospital patients 68% of community patients felt that there were sufficient supportive care services Concerning the overall quality of care received, 12.5% of community patients felt that their care had been extremely bad or less than average, compared with 0% of hospital patients; 4.6% of community patients thought that the care had been average, compared with 0% for hospital; and 83% of community patients felt that their care had been good or extremely good, compared with 100% of hospital patients Detailed results reported in paper Community respondents who were dissatisfied tended to be patients in smaller and low-volume clinics Also reported satisfaction with physician and chemotherapy nurses, satisfaction with amount of information provided before first hospital visit, availability of information, suggestions for improving the community programme

Study	Outcomes
NHS Bristol 2010[36]	*Questionnaire* When patients were asked if felt they were given sufficient privacy, 62% of outpatients said always, compared with 76% at the community health centre and 97% at home When asked if they received caring and sensitive nurse care 85% of outpatients said always, compared with 100% at the community health centre and 97% at home When asked about having sufficient opportunity to ask the chemotherapy nurse a question, 78% of outpatients said always, compared with 100% at the community health centre and 82% at home; 78% of outpatients said they always received an understandable reply, compared with 86% at the community health centre and 78% at home 87% of outpatients said they always had a clear explanation of impending medical procedures, compared with 95% at the community health centre and 87% at home Top five reasons for choosing treatment location: Outpatient: 1. Being with others receiving chemotherapy 2. Keeping to a routine 3. Access to support/added services 4. Getting to treatment 5. Access to doctor and medical staff Community: 1. Concern about hospital-acquired infections 2. Concern about waiting time 3. Travel costs 4. Getting to treatment 5. Car parking Home: 1. Concern about hospital-acquired infections 2. Getting to treatment 3. Car parking 4. Concern about waiting time 5. Being in familiar surroundings Total sample size = 118, but unclear how many in each setting

Results for preference outcomes

Study	Outcomes
Randomised trials	
Corrie *et al.* 2013[4]	*Questionnaire* 82% of patients expressed a preference for future treatment in the community: the proportions that would prefer any future treatment in the same location were as follows: outpatient 57%, GP surgery 81% and home 90%
King *et al.* 2000[31]	*Questionnaire (interview) on patient preference* Including only patients who completed both home and outpatient treatments: 29/40 (73%) of patients preferred treatment at home compared with treatment at hospital (95% CI 59% to 86%; $p = 0.01$). 11/40 (27.5%) of patients preferred hospital treatment 10/29 (34%) patients who preferred home treatment changed their preference to outpatient treatment if home treatment meant waiting another hour. 3/11 patients who preferred outpatient treatment changed their choice to home treatment if they had to wait an hour longer at hospital Including the 13 patients who chose not to be randomised because they preferred the outpatient setting, and the eight patients who dropped out after receiving outpatient chemotherapy during run-in (because they felt more secure at hospital): 29/61 (48%) of patients preferred home care (95% CI 35 to 60; $p = 0.61$) For trial recruits only (i.e. including the eight who dropped out during run-in): 29/48 (60%) of patients preferred home care (95% CI 47% to 74%; $p = 0.19$) *Self-administered questionnaire (carers)* Of 25 carers who completed the questionnaires, 17/25 (68%) preferred treatment at home (95% CI 50% to 86%; $p = 0.11$)
Pace *et al.* 2009[29]	*Two preference questions:* 1. Preferred location for remaining treatment: 30/31 (97%) patients chose outreach location when asked after first crossover period. One patient chose cancer centre as moving house and would be closer 2. Preferred location for all treatment: 30/31 (97%) patients said they would have preferred to receive all their treatment at the outreach centre. One patient preferred the cancer centre because of decor and gloomy atmosphere in outreach location
Christiansen *et al.* 2011[28]	*Questionnaire (patients)* Not reported
Rischin *et al.* 2000[32]	*Questionnaire (patients)* All 20 patients (100%; 95% CI 83% to 100%) preferred to have their remaining therapy given at home When asked where they would have preferred to receive their first two treatments if they had had their time again, 14/20 (70%) patients said they would have preferred both treatments at home [7/9 (78%) in the hospital-first group, 7/11 (64%) in the home-first group]; 2/20 (10%) said they would prefer the first treatment at home and the second in hospital [0 in the hospital-first group; 2/11(18%) in the home-first group]; 2 (10%) said they had no preference [1/9 (11%) in the hospital-first group, 1/11 (9%) in the home-first group]; and 0 patients said they would prefer both treatments at hospital
Stevens *et al.* 2006[55]	*Qualitative patient preference interviews* See qualitative data extraction
Remonnay *et al.* 2002[34]	*Questionnaire* 95% of all patients asked preferred chemotherapy treatment at home. Number of patients asked is not clear owing to dropouts

Study	Outcomes
Non-randomised studies	
Souadjian *et al.* 1992[48]	*Questionnaire* Authors reported that home was the preferred option for patients
Pong *et al.* 2000[37]	*Questionnaire: posted survey* $n = 153$ For the first treatment community patients chose whether to receive their first chemotherapy treatment at the hospital or community clinic. Almost half said that they had received their first treatment at the hospital Reasons for choosing community care: Community respondents ($n = 153$). Top three reasons from a given list were weighted on basis of choice. Top five reasons (in order) were: 1. Able to go home immediately after chemo treatment (weighted score 227) 2. Time required for travel to and from the cancer centre, i.e. main hospital (score 115) 3. Cost of travelling to and from the cancer centre (score = 93) 4. Support of family and friends in my community while receiving chemo treatment in local hospital (score = 74) 5. Receiving treatment close to home where my family physician is (score = 73) Perceived disadvantages of the community program Similarly, community patients were asked to pick the top three disadvantages of community care. 37% did not answer, many of whom said that they believed there were no disadvantages in participating in the programme. Top five responses: 1. There are no cancer specialists in my community (137) 2. The health professionals in my community may not be as up to date about cancer treatment as those at the hospital cancer centre (84) 3. The cancer centre in Sudbury (main hospital) is a new and more cheerful building than my local hospital (37) 4. There are more supportive care services at the cancer centre in Sudbury (31) 5. Not having enough contact with other cancer patients (31) See paper for full list of ranked answers Hospital patients' ($n = 114$) reasons for not participating in community programme: • 50% stated they were not eligible (< 50 km from hospital) • 23% said they had never heard of the programme (all but two of whom came from communities that had a community clinic and, thus, were eligible) • 27% said that they were eligible but chose not to take part. Of those, 75% felt that they would receive better-quality care at the hospital cancer centre. Some mentioned that they had switched back to the hospital after having 'bad experiences' with COCN programme (no numbers given) Also reported: information issues surrounding COCN programme (pp. 4–18)

Results for compliance outcomes

Study	Outcomes
Randomised studies	
Corrie *et al.* 2013[4]	*Proportions of patients receiving compliant dosing schedules* Unclear (17 did not complete 12 weeks of treatment mainly due to disease progression)
Borras *et al.* 2001[35]	*Proportions of patients receiving compliant dosing schedules* Unclear
Non-randomised studies	
Satram-Hoang and Reyes 2011[47]	*Proportions of patients receiving compliant dosing schedules* Rituximab + chemotherapy compliance with dosing schedule (once every 3 weeks for up to eight cycles): 34% in outpatient setting ($n = 541$) vs. 54% in community clinics ($n = 3149$); $p < 0.001$ *Number of cycles of chemotherapy delivered* • Community: 61% received < 6 cycles, 21% received 6–8 cycles and 18% received > 8 cycles • Outpatient: 77% received < 6 cycles, 12% received 6–8 cycles and 11% received > 8 cycles
Frølund 2011[41]	*Number of scheduled chemotherapy treatments completed (completed/scheduled):* • Patient 1: 10/24 • Patient 2: 20/24 • Patient 3: 16/16 • Patient 4: 14/24 • Patient 5: 14/16 • Patient 6: 13/24 *Number of chemotherapy treatments delivered at home:* • Patient 1: four • Patient 2: 11 • Patient 3: nine • Patient 4: six • Patient 5: seven • Patient 6: three

Results for safety outcomes

Study	Outcomes
Randomised studies	
Corrie *et al.* 2013[4]	*Adverse events* Four of 39 SAEs recorded during this study were assessed as being related to treatment setting
Borras *et al.* 2001[35]	*Adverse events* No data other than withdrawal details (see study characteristics) *Chemotherapy toxicity* No differences between groups for withdrawals due to toxicity (16 cases in total)
Pace *et al.* 2009[29]	*Adverse events* There were no adverse reactions during chemotherapy at any location. On one occasion a nurse was unable to cannulate a patient in the outreach centre; patient returned to cancer centre and was treated there *Chemotherapy toxicity* Measured with C-SAS The most common side effects were nausea, vomiting, fatigue, feeling weak and difficulty sleeping. These showed no significant differences between the locations (Fisher's exact test) No further data reported
Christiansen *et al.* 2011[28]	*Chemotherapy toxicity* There was no significant difference in treatment toxicity between the two groups ($p = 0.10$). 14.8% of patients treated at home had to be seen at the outpatient clinic for toxicity evaluation and prescription of chemotherapy, in particular due to difficulties in precise evaluation of hand-foot skin reactions by telephone interviews Mode of measurement not reported *Hospitalisation* 14.8% of patients treated at home had to be seen at the outpatient clinic (see toxicity)
Rischin *et al.* 2000[32]	*Complications* There were no major complications with the chemotherapy administration
Stevens *et al.* 2006[33]	*Adverse events* No statistically significant differences in overall adverse events. Regardless of treatment allocation, change of location resulted in significantly more adverse effects in patients who had no previous adverse events

Study	Outcomes
Non-randomised studies	
Lowenthal *et al.* 1996[45]	*Adverse events* 'Infrequent difficulties with venous access' 'One serious complication' – patient had dystonic reaction to drug (metaclopramide, an antiemetic), transferred to hospital for treatment but not admitted. The authors assumed equal effectiveness due to insignificant numbers of adverse events
Souadjian *et al.* 1992[48]	*Adverse events* 4/83 home chemotherapy patients had chemotherapy related adverse events requiring hospitalisation: two thrombosed catheters; one accidental catheter removal by patient; and one sepsis Data were not presented for the outpatient setting
Barker 2006[40]	*Chemotherapy toxicity* NB: seven outreach patients received 86 cycles of chemotherapy; seven patients received 112 cycles of home chemotherapy WHO toxicity grading scale: • Nausea: 15% of cycles in the home; 21% in the outreach clinic • Skin changes: 19% of cycles in the home; 49% in the outreach clinic • Diarrhoea: 25% of cycles in the home; 51% in the outreach clinic • Lethargy: 16% of cycles in the home; 62% in the outreach clinic The author stated that the results reported were 'examples of the results for the audit'
Pong *et al.* 2000[37]	*Postal questionnaire (hospital* n = *114, community* n = *153):* 40% of hospital respondents and 45% of community respondents reported that they had called for medical help concerning their chemotherapy. 29% of hospital patients who had called for help said they had encountered difficulty vs. 46% of community patients who said they also had encountered problems ($p < 0.01$)
Vergnenègre *et al.* 2006[49]	*Adverse events* Home: two adverse events in 24 cycles Hospital: seven adverse events in 30 cycles No statistically significant difference ($p = 0.27$)

C-SAS, Chemotherapy Symptom Assessment Scale; SAE, serious adverse event; WHO, World Health Organization.

Appendix 6 Costs data

Randomised studies	
Corrie *et al.* 2013[4]	Home: £2139 (SD £1590) GP: £2497 (SD £1759) Hospital: £2221 (SD £1831) ICER: GP vs. hospital = £16,235/QALY
King 2000[31]	(CEA study: cost consequences) Costs The net additional cost of home chemotherapy (per treatment) was AUS$68.81 This figure was the sum of: • additional nursing cost: $39.79 for time spent in organisation, preparation and clean-up • travel time: $19.90 • use of motor vehicles: $9.09 • special equipment required for home administration: $0.03 The total cost of establishing a new chemotherapy ward was estimated to be $70,581 ($5187 annual cost) A range of different estimates (reported in table) for the additional cost of a new ward per treatment were calculated, based on a range of treatments per annum, projected increase in workload (assuming full capacity of new ward is 1560 treatments per annum, based on current ward capacity), annual capital costs per treatment, and additional overhead and joint cost per treatment (assuming incremental cost is 20% of existing overhead allocation) On this basis it was estimated that home chemotherapy would be a less expensive means of expanding the service by up to 50% of the ward capacity (additional cost = $65.54 per treatment for establishing a new ward at 50% capacity is less than the cost of $68.81 per treatment for home care). So, if capacity could be expected to increase by 50% or more it would be less costly to set up a new ward The interest rate in this calculation was varied from 3% to 10%, which made no difference to the break-even point because the opportunity cost of capital accounted for only 7% of the costs of capital and overhead
Pace *et al.* 2009[29]	Service costs: Mileage cost per session = £12.83 Mileage costs per six-session cycle = £76.98 (assumes £0.53 per mile) Opportunity cost of travelling time for each nurse was £32.08 per clinic (using average pay for a specialist oncology nurse outside London = £29,538 per annum. Plus on-costs, this amounts to £15.11 per hour) Marginal cost per clinic session = £64.16 Marginal cost per cycle of six clinic sessions = £384.96 There was no charge for running the clinics in the community hospitals during the study Patient costs: Mean cost of travel to outreach centre = £4.85 Mean cost of travel to cancer centre = £8.77

Randomised studies	
	Based on travel costs per mile (£0.40 per mile, inland revenue rate) plus parking charges Patient-borne costs of travelling (including public transport costs) to: • outreach centre = £8.70 • cancer centre = £14.99 Additional/marginal cost to patient of £6.29 per session or £37.74 per cycle of six sessions to attend the hospital cancer centre
Stevens *et al.* 2006[33]	Costs were reported as median (*n*, range) in CAN$ Home (time 3, 6 months, before crossover): 1318 (*n* = 14, 298 to 6302) Home (time 5, 12 months, after crossover): 851 (*n* = 13, 147 to 8726) Hospital (time 3, 6 months, before crossover): 1409 (*n* = 11, 419 to 7342) Hospital (time 5, 12 months, after crossover): 1050 (*n* = 9, 29 to 10,278) No differences were statistically significant but there was a trend towards lower costs in the home group. The home group also had higher baseline costs (1795, *n* = 15, 327 to 7227) than the hospital group (1374, *n* = 14, 98 to 4381)
Rischin *et al.* 2000[32]	(CEA study: cost consequences) Costs Perspective: treating hospital Home chemotherapy was associated with an estimated average increased cost of $83 (95% CI $46 to $120; $p = 0.0002$) for each chemotherapy treatment, relative to the cost of chemotherapy in the hospital The average cost of the first course of treatment was estimated to be $57 more than the cost of the second (95% CI $20 to $94; $p = 0.004$) (non-setting specific). There was no carry-over effect ($p = 0.16$)
Remonnay *et al.* 2002[34]	Costs were reported in 1998 US$. Statistical significance was measured using Wilcoxon tests Costs of personnel for one chemotherapy administration Health-care personnel: home = 69.10 (SD 19.20) vs. outpatient = 51.70 (SD 10.60) ($p < 0.0001$) Co-ordination: home = 20.20 (based on assumption) vs. outpatient = 0 (assumption of no hospital costs) Other: home = 6.60 vs. outpatient = 3.30 Total: home = 95.80 (SD 19.20) vs. outpatient = 55.00 (SD 10.60) ($p < 0.0001$) Additional costs for health-care personnel at home were driven by the costs of physician home consultations ($19.8 for home vs. $7.8 for consultation) Medication costs All chemotherapy drugs: home = 136.70 (SD 81.90) vs. outpatient = 74.00 (SD 52.80) ($p < 0.0001$) Three most common regimens: AC: home = 169.10 vs. outpatient = 76.50 CMF: home = 76.20 vs. outpatient = 22.10 Navelbine: home = 140.5 vs. outpatient = 111.90 Other marginal costs for outpatient chemotherapy (per administration)

Randomised studies	
	Transportation 21.80 Laundering 6.10 Overhead costs Home = 20.10 vs. outpatient = 120.30 Total costs (marginal costs do not include overhead costs) Marginal: home = 232.50 (SD 81.80) vs. outpatient = 157.0 (SD 62.00) ($p < 0.001$) Average: home = 252.60 (SD 81.80) vs. outpatient = 277.30 (SD 62.00) ($p = 0.0002$) Sensitivity analysis of total costs assuming equal medication costs (home-care access to hospital pharmacy) Marginal: home = 170.00 (SD 58.20) vs. outpatient = 157.00 (SD 62.00) ($p < 0.001$) Average: home = 190.00 (SD 58.20) vs. outpatient = 277.30 (SD 62.00) ($p < 0.001$) Costs per hour or per tariff activity were provided in the paper
Non-randomised studies	
Grusenmeyer *et al.* 1996[42]	Home care: • 5-FU + leucovorin (5 days) $799 • Cyclophasphamide + doxorubicin $797 • Cisplatin + etoposide $2196 • Cisplatin, mitomycin + vinblastine $2063 • Hydration $308 • Transfusion $435 • Amphotericin $277 Hospital: • 5-FU + leucovorin (5 days) $151 • Cyclophasphamide + doxorubicin $249 • Cisplatin + etoposide $1096 • Cisplatin, mitomycin + vinblastine $1107 • Hydration $151 • Transfusion $359 • Amphotericin $181
Lowenthal *et al.* 1996[45]	Home treatment costs: Total cost per treatment: $49.93 Salary $36.39 (including 15% overhead, and travel time, at $24.38 per hour salary) Special equipment $9.11 (106 computer-activated drug-delivery devices at $29.66 each) Car expenses $4.43 (petrol, maintenance, insurance, registration and depreciation) Hospital treatment costs: $116.00 ($165.71 multiplied by the percentage of time spent administering chemotherapy) Marginal cost of delivering treatments at home The estimated costs of adding hospital capacity equivalent to the number of patients receiving home treatment was compared with the cost of delivering treatment at home. Chemotherapy was not evaluated independently for this analysis. Expanding capacity for the hospital assumed extending hours to 20.30 from 17.00 and paying a higher night wage for nurses ($29 per hour)

Randomised studies	
	Hospital $38,207 Home $45,767 Further details for the marginal analysis were provided
Souadjian *et al.* 1992[48]	All costs are in US$/treatment-day Home: • 5-FU (continuous infusion) $89 • CDDP (continuous infusion) $1113 • CDDP + ETOP + BLEO (rapid infusion) $1839 • CDDP + ETOP + FUDR (continuous infusion) $1730 • CARBO + ETOP + IFOS/mesna (continuous infusion) $3283 Hospital: • 5-FU (continuous infusion) $294 • CDDP (continuous infusion) $1348 • CDDP + ETOP + BLEO (rapid infusion) $2958 • CDDP + ETOP + FUDR (continuous infusion) $2414 • CARBO + ETOP + IFOS/mesna (continuous infusion) $4876
Hansson *et al.* 2013[38]	Feasibility study (home setting only): The daily hospital charge for a home visit was US$597 vs. $600 for an outpatient visit (The home-care operational costs, payroll costs and overheads were compared with the costs billed for an outpatient visit) The home-care cost included the following items: wages, fuel, uniforms, nursing-bags, parking, car, mobile telephone, various expenses, leasing of car, and medication. Costs (no resource use) were given for each of these items for 2 years
Pong *et al.* 2000[37]	Survey posted questionnaire: COCN, $n = 153$; NEORCC, $n = 55$ Costs reported in CA$ Transport costs Respondents were asked to estimate the total amount they spent on transportation for a typical trip to and from the hospital. Transport costs included costs of gasoline, car rental, bus fare, etc. Community patients: $44 (range $0–160) Hospital patients: $33 ($0–140) When removing individuals who did not incur any travel costs (e.g. driven by volunteers): Community: $49 (range $15–160) Hospital: $39 ($12–140) Total travel expenses (less any subsidies received from government travel grants), including cost of gas/car rental/bus fare, transportation and accommodation, food, lost wages and other expenses, vehicle operating and ownership expenses: Community patients: $294 (range $58–1010) Hospital patients: $188 (range $40–495) (All costs items reported disaggregated; see paper for more detailed costs)

Randomised studies	
	Travel time to community clinics was not considered as community patients lived within a relatively short distance from a clinic and so it was assumed the travel costs would be minimal NB: A budget impact model was also conducted. This has not been extracted as it was a non-comparative assessment (only looked at the cost impact at the hospital site and included non-unique costs)
Ingleby *et al.* 1999[44]	Costs in GBP (£) Mean weekly costs: Hospital: £230 (DeGramont), £92 (Lokich), £35.39 (Tomudex) Home: £135.27 (DeGramont), £41.77 (Lokich), £33.01 (Tomudex) Home setting additional costs: DeGramont: £689 Lokich: £311 Tomudex: £143
Vergnenègre *et al.* 2006[49]	Average cost per cycle was €2829.51 (95% CI €2560.74 to €3147.02) for hospital infusion, €2372.50 (95% CI €1962.75 to €2792.88) for home-based care (–16.15%). Difference was €–457.01 by cycle (95% CI –€919.74 to €26.82). Real costs by infusion for home was €484.42 (95% CI €424.18 to €540.32) vs. a fee of €699.89 (95% CI 643.64; 750.23) (–30.79%)

5-FU, 5-fluorouracil; AC, adriablastin (doxorubicin), endoxan (cyclophosphamide); BLEO, bleomycin; CARBO, carboplatin; CDDP, cisplatin; CEA, cost-effectiveness analysis; CMF, cyclophosphamide, methotrexate and 5-flourouracil; ETOP; etoposide; FUDR, floxuridine; IFOS, ifosfamide.

Appendix 7 Non-randomised study characteristics

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Barker 2006,[40] published paper Linked references: none Design: comparative audit Country: Wales Recruitment period: June 2004 to December 2004 Number of recruiting centres: unclear Assessment time points: over 6 months (no specific time points reported)	Key characteristics of recruited population: Inclusion criteria: colorectal cancer patients No other data reported Treatment intention: adjuvant Chemotherapy used: not reported	Setting details Home: no details reported Community: outreach chemotherapy clinic, no details reported Preparation of chemotherapy: not reported	Target sample size: not reported, but 14 patients were included Withdrawals and dropouts: not reported	Primary outcome(s): toxicity (WHO toxicity grading scale) Other outcomes: patient satisfaction Qualitative data reported? Yes Economic evaluation? No Comments: the pilot provided the background to the CHOICE project – Centre, Home and Outreach: Investigating Chemotherapy Environments. This project never got under way due to lack of funding
Main reference: Grusenmeyer *et al.* 1996,[42] conference abstract Linked references: none Design: not reported Country: USA Recruitment period: not reported Number of recruiting centres: not reported Assessment time points: not reported	Key characteristics of recruited population: colon, breast and lung cancer patients with short, medium and long treatment durations Treatment intention: unclear Chemotherapy used: 5-FU + leucovorin Cyclophosphamide + doxorubicin Cisplatin + etoposide Cisplatin, mitomycin + vinblastine	Setting details: Home Outpatient Preparation of chemotherapy: not reported	Target sample size: not reported Withdrawals and dropouts: not reported	Primary outcome(s): costs, patient satisfaction Other outcomes: none Qualitative data reported? No Economic data reported? No Comments: costs were not broken down by the type of cost. Patient satisfaction was reported only for outpatient chemotherapy

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Hansson *et al.* 2013,[38] full paper Linked references: Hansson *et al.* 2010[105] abstract; Hansson 2011[61] full paper; Hansson *et al.* 2012[67] full paper; Hansson *et al.* 2012[106] abstract Design: controlled, non-randomised study Country: Denmark Recruitment period: August 2008 to December 2009. Historical control patients: December 2007 to August 2008 Number of recruiting centres: one Assessment time points: at inclusion to the study and after 3 months	Key characteristics of recruited population: Inclusion criteria: Children aged < 18 years who had been diagnosed with any cancer at least 1 month prior to inclusion, with one parent fluent in Danish Gender male ≈ 50% Cancer type: acute lymphoblastic leukaemia/acute myeloid leukaemia/ lymphoma (≈70%); central nervous system tumour (≈10%); solid tumour (≈20%) Treatment intention: curative treatment Chemotherapy used: vincristine and dactinomycin. Chemotherapy lasted for no more than 10 minutes	Setting details: Home: home care was provided by two nurses who were employed specifically for home care. Visits lasted 15–19 minutes and, depending on the task performed, included one or both nurses. All preparations were made at the paediatric oncology ward Outpatient: hospital care consisted of standard care at the paediatric oncology ward, day-care unit or outpatient clinic, i.e. according to Nordic treatment protocols or European and international treatment protocols Preparation of chemotherapy: the authors reported that 'all preparations were made at the paediatric oncology ward'	Target sample size: not reported but 28 children received home chemotherapy and 47 children received outpatient treatment (35 historical, 12 concurrent) Withdrawals and dropouts: < 5% of the nurse referrals for home care were refused by the paediatric oncologist based on medical evaluation. For three out of 54 children home care was declined: two preferred to have treatment at the hospital as the treatment protocol only included a few hospital visits; one preferred to keep the home free from treatments 134 patients were eligible for the study. 45 home-care group children were approached and 31 (66%) initially participated, and 28 (90%) of those completed the 3-month questionnaires. 86 hospital-care group (concurrent and historical control) children were approached and 58 (68%) initially participated and 47 (81%) of those completed 3-month questionnaires None of the reasons for non-participation ($n = 38$) were setting-related	Primary outcome(s): not specified Other outcomes: patient and parent reported health-related quality of life (PedsQL Generic Core Scale and PedsQL Cancer Module); psychological impact on family (PedsQL Family Impact Module); cost Qualitative data reported? Yes (but only for home setting, reported in a separate study) Economic evaluation? Yes Type of economic evaluation: CEA Currency (price year): US$ and DKK (not reported) Economic perspective: hospital (not explicitly reported) Comments: home-care patients had to live within 50 km of the hospital. Concurrent outpatient care patients had to live more than 50 km from the hospital (but historical controls did not) The study also included a case series feasibility study which assessed safety and parent and child satisfaction and preference of treatment for home-care families

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
				The controlled study included two control groups: (1) historical standard-care control group (8-month period before the home-care programme started, regardless of distance to hospital); and (2) concurrent standard-care control group. Controls (1) and (2) were combined (to increase the sample size) for statistical analysis The authors stated that, of the home-care visits, 86% replaced an outpatient visit and 14% replaced an inpatient visit
Main reference: Herth 1989,[43] full published paper Linked references: Herth 1987[107] (unobtainable Ph.D. thesis) Design: non-randomised trial Country: USA Recruitment period: not reported Number of recruiting centres: not reported Assessment time points: not reported	Key characteristics of recruited population: Eligibility criteria: Adults (> 21 years) currently receiving (appropriate) chemotherapy and English literate were eligible Gender: around 44% were male (based on whole study population, which included some inpatients) Cancer type: varied, but little detail given – breast (28%) and lung cancer (19%) were the most common (based on whole population) Mean age: around 50 years (range 21–85 years)	Setting details: Home: no details reported Outpatient: no details reported Preparation of chemotherapy: no details reported	Target sample size: unclear, but appeared to be 40 in each setting Withdrawals and dropouts: unclear whether there were any	Primary outcome(s): hope (Herth Hope Scale); coping (Jalowiec Coping Scale) Other outcomes: none Qualitative data reported? No Economic evaluation? No Comments: two patients declined to take part Age and extent of illness were not identified as confounding variables

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
	Mean time since diagnosis: around 19 months Treatment intention: 50% of patients had local disease (curative) and 50% had metastases (palliative) Chemotherapy used: not reported			
Main reference: Ingleby *et al.* 1999,[44] conference abstract Linked references: Ingleby *et al.* 1999,[71] abstract Design: cohort study (with retrospective control group) Country: England Recruitment period: not reported Number of recruiting centres: not reported Assessment time point: 12 weeks	Key characteristics of recruited population: Patients with advanced colorectal cancer Treatment intention: not reported Chemotherapy used: Lokich 5-FU; DeGramont 5-FU and folinic acid; Tomudex©	Setting details: Home: one senior oncology nurse was responsible for treatment and assessment of the patient with back-up from medical staff as required Hospital outpatient: preparation of chemotherapy: not reported	Target sample size: 25 patients were recruited Withdrawals and dropouts: 16 patients completed 12 weeks of treatment	Primary outcome(s): costs Other outcomes: patient preference (though no results presented in abstracts) Qualitative data reported? No Economic evaluation? No Comments
Main reference: Lowenthal 1996,[45] published paper Linked references: N/A Design: retrospective audit of service over 5 years Country: Australia Recruitment period: 1989–94 (cost analysis 12 months only) Number of recruiting centres: one	Key characteristics of recruited population: All patients with 'satisfactory home circumstances' and receiving chemotherapy which non-platinum based chemotherapy were eligible Patient characteristics were reported only for diagnosis, and only for the 12-month cost-comparison period Gastrointestinal: 47/184 (25%)	Setting details: Home: counselling, education and support provided at hospital, received same follow-up as hospital patients. Note that 'home' also included patient workplaces, GP offices and day-care centres Outpatient: hospital day patients: no details reported	Target sample size: not reported. 179 patients were included Withdrawals and dropouts: not reported	Primary outcome(s): safety (major complications requiring patient be transferred and admitted to hospital), costs, resource use Other outcomes: N/A Qualitative data reported? No Economic evaluation? Yes Type of economic evaluation: CEA (CMA)

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Assessment time points: clinical effectiveness was not formally assessed Cost analysis was conducted for the 12 months before 30 November 1994. Running costs for the outpatient hospital ward were calculated from 1 July 1994 to 31 December 1994 and extrapolated to a full year	Lymphoma: 49/184 (27%) Breast: 35/184 (19%) Lung: 11/184 (6%) Myeloma: 19/184 (10%) Non-malignant/autoimmune: 7/184 (4%) Miscellaenous solid tumours: 16/184 (9%) Treatment intention: not stated, cytotoxic chemotherapy given for cancer and blood disorders Chemotherapy used: flourouracil with/without folinic acid; intravenous methotrexate; cyclophosphamide, methotrexate and fluorouracil with/without prednisolone; cyclophosphamide, vincristine and prednisolone; cyclophosphamide, doxorubicin, vincristine and prednisolone; mitozantrone; hoelzer protocol; interferon; doxorubicin and cyclophosphamide; epirubicin and cyclophosphamide; fluorouracil, epirubicin and cyclophosphamide; vinblastine; cyclophosphamide alone; other	Preparation of chemotherapy: no details reported		Currency: AU$ (1994) Economic perspective: hospital Comments: there was a lack of clear reporting on participant numbers and treatments for the 5-year audit The 1-year cost comparison was more clearly reported (65 patients were treated at home (1486 visits); 119 patients were treated in the hospital day ward) No comparative data in terms of safety were reported for the hospital patients; this was stated to mean treatment at home is safe

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Mitchell 2011,[39] full report on interview element Linked references: Mitchell 2013,[50] published paper Design: comparative audit of service provision Country: England, UK Recruitment period: not reported (data collected January to October 2010, service initiated in 2007) Number of recruiting centres: one Assessment time points: survey given out at fourth treatment and returned by stamped addressed envelope	Key characteristics of recruited population: Eligible patients lived more than 15 miles from the oncology centre, required treatment from an approved list that would take less than 3 hours to administer, and had not reacted adversely to the first treatment (given in centre) Male: 6/20 (30%) Mean age: 61 years (range 46 to 76 years) Cancer type: • Colorectal: 10/20 • Breast: 5/20 • Pancreas: 2/20 • Lymphoma: 1/20 • Larynx: 1/20 • Rare vascular: 1/20	Setting details: Community: mobile chemotherapy unit (bus) where treatment is nurse-led. Bus is driven to five community hospitals (one per day of the week) for administration of treatment by experienced oncology nurses with additional chemotherapy training. Patients travel directly to the venue nearest to their home Five-patient capacity on board Two nurses per bus. Treatment capacity: 12 patients intravenous chemotherapy and four patients oral chemotherapy per day If fewer than four patients are booked then the service is cancelled (or due to staff sickness) Hospital (outpatient): outpatient clinic	Target sample size: 20 (first 20 to respond were interviewed as planned) Withdrawals and dropouts: not reported for the survey. All patients who indicated an interest in being interviewed took part	Primary outcome(s): qualitative data from in-depth interviews focusing on experience of having treatment in different locations Other outcomes: questionnaire measuring: service satisfaction; transport details and costs; companion costs; cost of childcare/missed work Qualitative data reported? Yes Economic evaluation? No Comments: the survey component does not appear to have been reported or published as yet; author has been contacted Bus was donated by a charity 'Hope for Tomorrow' and they also maintain the unit. NHS funds the nurses, driver and fuel

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
	Treatment intention: not reported Chemotherapy used: • Carboplatin • GemCarbo (Gemcitabine and Carboplatin) • Trastuzumab • Zoledronic acid • FEC (fluorourcil, epirubicin and cyclophosphamide) • Gemcitabine • GemCap (gemcitabine and capecitabine) • ECF (epirubicin, cisplatin and fluorourcil) • Capecitabine • Vinorelbine • VinCarbo (vinorelbine and carboplatin) • Pemetrexed • FF (fluorourcil and folinic acid) GemCis (gemcitabine and cisplatin)	All patients had the first treatment in clinic so that any adverse reactions could be observed Preparation of chemotherapy: appears to be prepared at the general hospital and collected along with the staff by the mobile unit on the day of treatment		
Main reference: NHS Bristol 2010,[36] unpublished report of pilot study Linked references: none Design: non-randomised trial Country: England Recruitment period: March 2009 to February 2010 Number of recruiting centres: one Assessment time points: not reported	Key characteristics of recruited population: A wide range of patients were treated, though most had breast, lung, ovarian or gastrointestinal cancer Treatment intention: mixed Chemotherapy used: only treatments lasting up to 4 hours. A wide range was listed in an appendix	Setting details: Home: given by a private provider Community: a community health centre (care delivered by the hospital team) Outpatient: Bristol Haematology and Oncology Centre Preparation of chemotherapy: not reported	Target sample size: 220 home patients Report written when 165 patients had received home treatment 556 had outpatient treatment and 127 had community treatment Withdrawals and dropouts: only a random sample of patients were sent a questionnaire regarding patient experience. 118 questionnaires were returned – 'a return of 45%'. Therefore, the total random sample was 262 patients	Primary outcome(s): not reported Other outcomes: patient experience Qualitative data reported? No Economic data reported? No Comments: the community setting had also been evaluated in an earlier 2008 study (further details not available)

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Payne 1992,[46] published paper Linked references: Payne 1992,[108] published paper Design: non-randomised trial Country: England Recruitment period: April 1986 to September 1987 Number of recruiting centres: one Assessment time points: monthly, for 6 months	Key characteristics of recruited population: consecutive patients with advanced breast or ovarian cancer were referred to the centre Mean age: approximately 57 years Cancer type: breast 36/53 (68%); ovarian 17/53 (32%) Treatment intention: palliative Chemotherapy used: hospital patients received standard dose chemotherapy, while home patients received low-dose intermittent palliative chemotherapy. Specific drug regimens were not described	Setting details: Home: patients allocated to home chemotherapy had a central venous catheter installed for home treatment Outpatient: no further details of delivery were provided for either setting Preparation of chemotherapy: no details of chemotherapy drug preparation provided	Target sample size: not reported; 53 participants were recruited Withdrawals and dropouts: four at home withdrew due to illness; eight in hospital withdrew owing to illness Seven at home and six in hospital died during, or immediately after the 6-month study period	Primary outcome(s): Quality of life: a bespoke tool was constructed with four domains – Psychological Stress, Physical Complaints, Marital Satisfaction and Activity Other outcomes: individual subcomponents of the four domains were reported, including HADS, physical symptoms, and Karnofsky Perfomance Scale Qualitative data reported? No (see linked paper; however, focus on coping strategies without distinction between settings) Comments: six patients refused to participate, mostly due to feeling too ill. The authors noted that any QoL differences may be due to differences in disease severity
Main reference: Pong 2000,[37] full published report Linked references: none Design: non-randomised retrospective comparative cohort study Country: Canada (north-eastern Ontario)	Key characteristics of recruited population: Inclusion criteria for community clinic: Patients must usually live at least 50 km from the hospital, but other factors such as health status and treatment complexity were considered	Setting details Community: clinic [Community Oncology Clinic Network (COCN) Program, launched 1994] Medical assessments were undertaken by local physicians and chemotherapy by community chemotherapy nurses at 19 community oncology clinics. Patients attended the hospital or one of three designated peripheral community clinics for follow-up visits	Target sample size: random sample of 210 community patients and 225 hospital patients from the OPIS database Withdrawals and dropouts: for the survey, the initial samples were reduced to 180 community patients and 190 hospital patients due to incorrect mailing addresses, deaths, etc.	Primary outcome(s): not specified Other outcomes: self-reported health status (seven-category Likert scale); patient travel patterns and costs; patient satisfaction; availability and use of education and supportive care services; reasons for choosing community/hospital setting and main perceived disadvantages; information issues; staff workload and time; budgetary impact; staff opinions

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Recruitment period: May 1999 Number of recruiting centres: one Assessment time points: unclear (but appeared to be after treatment course)	'Recent' patients were selected in order to minimise recall bias (no further details given) Male ≈ 44% Mean age ≈ 58.5 years Cancer type: Gastrointestinal (≈ 40%) Breast (≈ 30%) Haematological (≈ 10%) Lung (≈ 6%) Gynaecological (< 5%) Genitourinary (< 5%) Head and neck (< 2%) Skin (< 1%) Other (≈ 5%) *apart from marital status there were no significant differences between groups on any baseline characteristic Treatment intention: unclear Chemotherapy used: no specifics reported. Included drugs taking < 1 to > 4 hours to administer	Hospital outpatient: North-eastern Ontario Regional Cancer Centre (NEORCC) No details reported All patients had their first appointment at the hospital after diagnosis. Patients were given the option to have their first chemotherapy treatment at the hospital (given directly) or community clinic (if applicable). Treatment setting was dependent on patient distance from hospital and patient choice) Preparation of chemotherapy: not reported	Questionnaires were completed by 153/180 (85%) of the community sample and 114/190 (60%) of the hospital sample	Qualitative data reported? No Economic data reported? No Comments: the programme aimed to enable patients in remote communities to receive chemotherapy closer to home (unlikely to generalise to UK context) Very detailed report

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Satram-Hoang and Reyes 2011,[47] conference abstract Linked references: none Design: retrospective database cohort study Country: USA Recruitment period: patients diagnosed between 1 January 1998 and 31 December 2007 Number of recruiting centres: N/A Assessment time points: not reported	Key characteristics of recruited population: Inclusion criteria: Patients aged > 66 years with follicular lymphoma enrolled in Medicare Part A and B Mean age: 75 years Gender: male 45% Disease stage: stage IV: 39% (hospital); 34% (community clinic) Treatment intention: not reported Chemotherapy used: not reported. Only 74% of patients received any chemotherapy (others were treated with rituximab alone)	Setting details: Community (clinic): no details reported Hospital (outpatient): no details reported Preparation of chemotherapy: not reported	Target sample size: unclear, but around 3500 patients were studied Withdrawals and dropouts: not reported	Primary outcome(s): not specified Other outcomes: time to treatment initiation; duration of treatment; number of cycles delivered; compliance Qualitative data reported? No Economic evaluation? No Comments
Main reference: Souadjian *et al.* 1992,[48] conference abstract Linked references: none Design: unclear, but observational Country: USA Recruitment period: not reported Number of recruiting centres: one Assessment time points: not reported	Key characteristics of recruited population: not reported Treatment intention: not reported Chemotherapy used: 5-FU (continuous infusion) CDDP (continuous infusion) CDDP + ETOP + FUDR (continuous infusion) CDDP + ETOP + BLEO (rapid infusion) CARBO + ETOP + IFOS/mesna (continuous infusion)	Setting details: Home Hospital (outpatient) No details were given about either setting Preparation of chemotherapy: not reported	Target sample size: not reported; 83 patients had home chemotherapy; the number of outpatients was not stated Withdrawals and dropouts: not reported	Primary outcome(s): costs Other outcomes: complications; QoL; setting preference Qualitative data reported? No Economic evaluation? No Comments: it was not clear how the costs for outpatient chemotherapy were calculated

General details	Population and treatment	Setting	Recruitment and participation	Outcomes reported/comments
Main reference: Vergnenègre 2006,[49] full published paper Linked references: none Design: non-randomised trial (assignment criteria not reported) Country: France Recruitment period: not reported Number of recruiting centres: one Assessment time points: not reported	Key characteristics of recruited population: Grade IV non-small cell lung cancer Sufficient life expectancy for three cycles Age (mean): 58 (home 54; outpatient 62) Eligibility for home treatment: within 30 minutes' drive from hospital; carer/family able to support home treatment; agreement from GP Treatment intention: unclear Chemotherapy used: cisplatine and gemcitabine	Setting details: Home (day 8): Within 30 minutes' drive from hospital First dose in outpatient setting on day 1, second dose at home on day 8 Outpatient (days 1 and 8): no details reported Preparation of chemotherapy: no details reported	Target sample size: 20 *Outpatient:* 10 *Home:* 10 Withdrawals and dropouts: not reported	Primary outcome(s): mean cost per cycle Other outcomes: adverse events (grade III or IV toxicity) Qualitative data reported? No Economic evaluation? Type of economic evaluation: CEA Currency: EUR€ (price year not reported) Economic perspective: health service Comments

5-FU, 5-fluorouracil; BLEO, bleomycin; CARBO, carboplatin; CDDP, cisplatin; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; DKK, Danish Krone; ETOP, etoposide; FUDR, floxuridine; IFOS, ifosfamide; N/A, not applicable; OPIS, Oncology Patient Information System; QoL, quality of life; WHO, World Health Organization.

Appendix 8 Qualitative data extraction summary

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Bakker *et al.* 2001[57] Canada Linked references: an additional comparative quantitative paper was mentioned but unobtainable Perspectives: patients	Aim: to gain an understanding of cancer patients' experienced of receiving chemotherapy at community clinics Methodology: not reported Sampling: participants were purposively sampled to cover each of the 13 community chemotherapy clinics	Population: all patients living in the area were given the choice of treatment at the regional cancer centre or at a community clinic, of these, 28 were interviewed Data collection: unstructured interviews conducted in the patient's home with a research assistant. Interviews were taped and transcribed Patients were asked about receiving treatment at the community clinic, and were asked to compare this experience with visits or appointments at the regional centre including examples of the advantages or disadvantages	Demographic data were collected and summarised Thematic analysis of the interviews using transcripts. First three interviews reviewed by full research team, subsequently analysed by two researchers. Emergent themes and coding categories were described and line-by-line coding used Coding framework and examples were discussed with the wider research team	Of the 28 who began community treatment, two chose to return to the regional cancer centre to finish their treatment Two key themes emerged: Balancing gains and losses: Perceived differences in cancer treatment were grouped under QoL (travel time, lifestyle management, disruption) and biomedical care (technical competence, access to information, interaction with other patients) and participants seemed to trade these off when making the decision about where to have their treatment Communication links: This referred to communication between patients and health-care providers, as well as between health-care professionals at the different treatment locations. Patients felt it was easier to establish rapport with community staff. Although regional centres were associated with greater expertise, patients were willing to trade off so long as clear evidence of communication links with cancer specialists (e.g. telephone, fax, computer) Most patients preferred gains in QoL over medical expertise

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Butler 1984[59] California, USA Linked references: none Perspectives: patients and their family	Aim: unclear, appears to be an audit of a new service providing home care Methodology: not reported Sampling: unclear, 15 patients were mentioned as receiving the new treatment and all were asked about their experiences	Population: *n* = unclear although 15 patients are mentioned, some of whom received outpatient treatment and others experienced treatment at home Equal numbers of men and women. Ages ranged from 30 years to 65 years Data collection: questions about experience of treatment were included in routine outpatient review appointments with the oncology clinical nurse specialist	Not reported	Patients indicated that their QoL, was improved when they had control over their daily activities Hospitalisation for chemotherapy was disruptive and prevented a sense of normality. Access to regular support systems was interrupted by hospitalisations Home chemotherapy improved many of these aspects but patients were concerned about the functioning of the catheter and pump
Main reference: Corrie *et al.* 2013[4] UK Linked references: Corrie *et al.*,[98] Corrie,[99] Corrie *et al.*,[100] Corrie (2013, Cambridge University Hospitals NHS Foundation Trust, unpublished document) Perspectives: patients; health-care professionals	Aim: to assess experience of the treatment from patient and staff perspectives Methodology: framework (no further details reported) Sampling: patients purposively sampled for maximum variation, staff sampling not reported Protocol mentions selecting one in every 10 patients plus their carer, but unsure if this was successful or how many took part	Population: patient participants were taking part in a three-arm RCT comparing home, community and outpatient treatment. Included curative, palliative and supportive care (see *Appendix 3* for more details) 11 patients; five consultant oncologists; three GPs; five chemotherapy nurses; two hospital pharmacists and two senior managers Data collection: semistructured interviews conducted before treatment and after 12 weeks of treatment with patients. Interviews were recorded and transcribed	Matrix-based framework analysis approach	Most patients expressed support for their treatment location regardless of setting. Most patients expressed a preference for future treatment in the community. Notably, many patients declined to be randomised due to strong prior preferences Clinical staff were concerned about patient and staff safety, particularly in relation to the home environment. The hospital and GP settings were seen as more secure Although attitudes to safety concerns improved during the trial, this was not reflected in increased patient referrals All groups felt that community treatment offered patients convenience but raised concerns about affordability

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Crisp 2010[60] Canada Linked references: none Perspectives: patients	Aim: to explore and describe the perspectives of cancer patients receiving active treatment who chose to receive or refuse home chemotherapy Methodology: interpretive description Sampling: convenience sampling by nurses from the Cancer Treatment at Home pilot programme conducted by Alberta Health Services	Population: plan was to interview five who accepted home treatment and five who refused it, but impossible to recruit those who declined treatment at home and so additional accepters were recruited for a total of 10 participants Vignettes of all participants presented, context was large metropolitan area Length of treatment ranged from months to 4 years. Both curative and palliative treatments were given Data collection: semistructured interviews, recorded and transcribed plus field notes. Took place in patient's home or at the Cross Cancer Institute Nine interviews analysed (one lost due to technical problems)	Constant comparative analysis and ongoing engagement with the data, focused on inductive analysis. Use of transcripts, research notes, in-process diagrams and audio recordings Analysis followed each interview with key concepts being added to a master board. Researcher and supervisor both involved in process Summaries of research results offered to participants	Home was identified as being a 'natural habitat' in which they were better able to adapt to their circumstances. Patients were better able to redistribute their resources including time, energy and finances in ways that were meaningful. They felt that the care provided was enhanced and they were more receptive to teaching. Lastly patients viewed themselves as less ill and were better able to cope with their treatments
Main reference: Frølund 2011[41] Denmark Linked references: Frølund 2011,[41] full published paper, quant results Perspectives: patients	Aim: to examine how patients experience chemotherapy at home, and how it affects their everyday lives Methodology: not reported Sampling: all patients in the case series were included	Population: six patients (50% male, aged between 63 years and 73 years) taking part in the case series, all with experience having treatment both in hospital and at home All were diagnosed with bone marrow cancer in 2009 Supportive care treatment	Paul Ricoeurs hermeneutic phenomenology • A naive reading, first reading • A structural analysis, coding for meaning units using direct quotations • A critical interpretation and analysis of units and codes	Six main themes identified: patients preferred home treatment over hospital treatment; patients are less fatigued and stressed; home treatment has less adverse impact on patients' daily lives; patients have more energy left over for social relationships; patients feel less medicalised and accordingly home treatment increases quality of life

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
		Patients were scheduled to receive either 16 or 24 treatments; home treatment was given between 3 and 11 times Data collection: semistructured interviews recorded and transcribed Refers to Steinar Kvale		Having experienced nurses from the oncology department provides a sense of security
Main reference: Hall 2008[30] UK Linked references: none Perspectives: patients	Aim: to compare the experience of receiving chemotherapy at home vs. in hospital Methodology: humanistic approach/ phenomenology Sampling: all patients in the trial were included	Population: 15 patients were randomly allocated to treatment groups: 10 received treatment at home and five in the hospital. All patients were interviewed. See *Appendix 3* for more details Data collection: semistructured interviews (timing unclear) were recorded and transcribed	Thematic analysis (Bowling 1997)	Quality of life was an important factor in how care was perceived by patients. Both groups expressed satisfaction with the quality of their care; however, variations were also present in service provision Theme: comfort and security Theme: privacy Theme: practicalities Theme: relationships Patients treated at home were more strongly positive about their experiences and felt that it should be an option offered to all patients

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Hansson 2011,[61] Ph.D. thesis Denmark Linked references: Hansson *et al.*,[38] non-randomised trial report; Hansson *et al.*,[67] qualitative paper; Hansson 2010,[105] abstract; Hansson 2011, Hansson 2012,[106] abstract Perspectives: patients (children) and family members	Aim: to describe family members' experiences of a hospital-based home-care programme for children with cancer Methodology: descriptive inductive method Sampling: purposively sampled families from a pool of 53 children. Sample was based on differences in diagnosis, family constellation, parents' occupation, number of home-care visits and duration of treatment programme	Population: 14 parents representing 12 families were invited, of which two declined. 11 interviews conducted, recorded and transcribed Detailed sample characteristics and eligibility given in page 61 of full paper Number of home-care visits 9–66. Duration of treatment 3–16 months Data collection: unstructured interviews were recorded and transcribed Location and family member involvement in interview was chosen by the parents (six at home, five in hospital) Both parents = three families One parent = six families Both parents individually = one family Child and sibling = five families	Transcriptions were analysed using Graneheim and Lundman (2004) methods. Content analysis used as an interpretative process for analysing written communication. Focused on differences and similarities in the text Analysed using concepts of meaning units, codes, subthemes and themes Four steps: All authors read each interview several times Transcript divided into meaning units by first authors, each meaning unit then condensed into a description Condensed meaning units are labelled with codes, abstracted and compared for similarities and differences by all authors Each subtheme critically read, compared and a main theme formulated with is thread of underlying meaning Preliminary interpretations and themes presented to peers for discussion and credibility checking	Main theme: supporting the family to remain intact throughout the childhood cancer trajectory Subthemes: 'Decreasing the strain on the family and ill child' 'Maintaining normality and an ordinary life' 'Fulfilling the need for safety and security'

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Hjorleifsdottir *et al.* 2008[64] Iceland Linked references: Hjorleifsdottir *et al.* 2007[109] Perspectives: patients	Aim: to explore perceptions of care and service provided in an outpatient setting (also looked at experience of having cancer and coping strategies) Methodology: inductive qualitative Sampling: oncology nurses selected patients to be approached for the study, more than one hospital clinic included	Population: $n = 25$ Having radiotherapy or chemotherapy in an oncology outpatient clinic 16 women, nine men (mean age = 55 years, SD 13 years). 60% receiving chemotherapy, 40% receiving radiotherapy Curative ($n = 16$), symptom control ($n = 8$), palliation ($n = 1$) Data collection: semistructured interviews carried out in preferred location (most chose private room at oncology clinic). Recorded and transcribed Interview questions reported	Manifest and latent content analyses used. Detailed descriptions provided. Most analysis carried out by one authors working from transcripts using verbatim quotations and pre-established categories. Three other authors also read the analysis during the process and contributed ideas and discussion	Findings: Satisfaction in the outpatient clinic depended on delivery of drugs, caring attitudes of the health professionals and the caring encounters Negative factors included waiting times, difficulty parking and the clinic environment however there was tolerance around other patients sometimes needing more time with a doctor Other sections of the results focused on the impact of the diagnosis, coping strategies including attempting to maintain normality and keeping the uncertainty at a distance (only those findings relating to care received and satisfaction with outpatient setting extracted)
Main reference: Iredale *et al.* 2011[51] UK (Wales) Linked references: none Perspectives: patients	Aim: to determine who was using the bus (mobile cancer support unit) and explore their perceptions of having treatments on the bus Methodology: not reported (part of a mixed-methods project with a quantitative survey plus interviews) Sampling: all patients were invited to participate in interviews	Population: six chemotherapy patients and four social care patients took part. The bus provided both chemotherapy and social care services Data collection: bus visitors were given a survey to complete and also invited to attend follow-up interviews Semistructured interviews with questions informed by prior interviews with Tenovus (cancer charity) and Velindre (hospital) staff took place in patients' homes. Recorded and transcribed	Thematic analysis (no further details)	Most patients spoke very highly of the bus both based on first impressions and interior appearance and cleanliness Bus was said to be more convenient, more personal and more organised in comparison to previous treatment experiences Treatment on the bus was reported to save time and money, with reduced levels of stress and anxiety As confirmed by author, all quotations and comments on service were from chemotherapy patients

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
		Aimed to capture first impressions, experiences of treatment and comparison with previous treatment elsewhere		
Main reference: Kelly *et al.* 2004[62] UK Linked references: none Perspectives: patients; health-care professionals	Aim: examine the existing outpatient chemotherapy provision and assess the feasibility of providing a home-based chemotherapy service Methodology: not reported Sampling: targeted convenience sampling of patients with colorectal cancer as their treatment likely to be more amenable to home chemotherapy Purposive sampling of health-care professionals based on role and experience	Population: five patients with colon cancer currently undergoing outpatient chemotherapy with 5-FU 12 health-care professionals; consultant oncologists, chemotherapy nurses, pharmacist, nursing directorate and financial managers and local commissioner of cancer services Data collected between February and April 2000 Data collection: semistructured interviews recorded and transcribed Patient interview topics included: experiences of outpatient service (travel, side effects, general satisfaction), financial impact of illness/treatment and views on the proposed home chemotherapy service Health-care professionals were asked about opinions on current service, contracting and cost issues and feasibility of a home service	Transcripts were analysed thematically on a line-by-line basis by two researchers working independently Exemplar quotes were identified and interview themes were then integrated with contract and cost data from the rest of the paper (mixed methods)	Views on current service provision: All patients were generally satisfied with their care. Any negative comments related to waiting and journey times (all patients reported being delayed by up to 5 hours on at least one visit) Health-care professionals expressed concerns about waiting times and current service configuration, physical set-up contributed to problems Views on home-based chemotherapy: Patients reported a mixture of views; some felt that it would be a good idea and would reduce travel time with treatment given in a familiar and private setting. Some patients expressed concerns about safety and need for expertise from staff Health-care professionals were interested at least in theory in the provision of home chemotherapy. They raised concerns about funding, practicalities of patient numbers and increased demand Specific points relating to changes were made including the need for structured development and reference to local Cancer Networks

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Mitchell 2011[39] UK Linked references: Mitchell 2013,[50] published paper Perspectives: patients and partners	Aim: to explore experiences of people with cancer who received chemotherapy treatment in outpatient clinic and/or on board the MCU Methodology: interpretive phenomenological approach Sampling: convenience sampling, first 10 to respond to invitation in each setting were interviewed	Population: $n = 20$ Ten patients attending the mobile cancer unit, 10 attending the outpatient clinic Data collection: in-depth interviews in patient's home ($n = 19$) and in researcher's home ($n = 1$). In some cases spouses or partners were also involved All interviews were recorded and transcribed. Interviews lasted between 1 hour and 3 hours An interview journal was also kept to record notes on context and body language	Thematic phenomenological analysis involving three readings of the transcripts to familiarise, code words/ sentences/paragraphs, and then to allocate codes to new or existing categories Exemplary statements for each category were collected. Analyses were verified through discussion with a colleague Themes were developed from the categories	Only the findings relating to the process of receiving chemotherapy were presented, although participants told of their full journey through symptoms, diagnosis, referral and treatment Theme: in it together Theme: car parking and travel Theme: waiting for treatment in clinic Theme: having chemotherapy on the MCU Theme: privacy, dignity and safety The cancer and chemotherapy journey was described as being undertaken by the participant and their significant other. Available car parking and travelling impacted on quality of life, as did the environment and accessibility of nurses to discuss issues with participants. The most important, distinguishing feature between receiving chemotherapy in outpatient clinic and the MCU was the amount of time spent waiting. Having treatment on the MCU was perceived to be less formal and, therefore, less stressful. Participants reported significant savings in time spent travelling, waiting and having treatment, expenditure on fuel and companion time and costs

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: McIlfatrick *et al.* 2007[63] Northern Ireland, UK Linked references: none Perspectives: patients	Aim: to explore patients' experiences of having chemotherapy in a day-hospital setting Methodology: not reported, based on Meleis's theory of nursing transitions Sampling: convenience sample of patients who had experienced at least one cycle of chemotherapy as an outpatient and as an inpatient	Population: $n = 30$ Ages ranged from 21 years to 77 years; seven different cancers included; 50% had ovarian cancer; range of chemotherapy treatments given Data collection: semistructured interviews conducted in a private room in the day hospital, recorded and transcribed. Topic areas were reported	Narrative analysis was used, specifically Polkinghorne's two-stage process. Generalised paradigmatic analysis of narratives followed by an in-depth analysis of the narratives Member checks were used to establish 'trustworthiness', eight patients were asked to comment on themes following analysis Analysis was carried out by one researcher and checked by another and coding was performed by two blinded researchers. Agreement on themes and narratives was generally reported	Findings: Four key themes were identified: Facing the situation *Perceptions of the day hospital (positive sense of normality vs. negative dehumanising)* *System issues (environmental and organisational)* Looking ahead The themes in italics above relate directly to this review and these results were extracted in full
Main reference: Pace *et al.* 2009[29] UK (England) Linked references: Pace *et al.*[102] Perspectives: patients	Aim: a randomised comparison (crossover) of outpatient and community chemotherapy that included a satisfaction outcome Methodology: not reported Sampling: all participants selected for the trial (see *Appendix 3*)	Population: two patients took part in the trial, of which 11 provided additional information on their experiences Data collection: Chemotherapy Patient Satisfaction Questionnaire which includes an open-ended question	Examples of feedback were provided from four patients	Patients mentioned less waiting time, ability to maintain normality and reduced tiredness following treatment as a consequence of community-based treatment
Main reference: Rischin *et al.* 2000[32] Australia Linked references: King 2001[54] Perspectives: patients	Aim: to determine patient preferences between hospital- and home-based chemotherapy Methodology: not reported Sampling: all eligible randomised patients who completed treatment were included	Population: 20 participants who completed the RCT and returned their questionnaires. (See *Appendix 3* for more details) Data collection: questionnaire administered after two treatments (crossover design ensured all patients would have experienced both settings) to 20 patients Questionnaire included open-ended questions about 'any perceived difficulties or advantages of treatment in hospital or home'	Not reported; summary lists of reasons and comments were provided	No concerns relating to chemotherapy in the home were reported, some patients reported problems with hospital treatment (transport difficulties and waiting times) Almost all of the patients listed advantages to being treated at home; only one patient felt that there were advantages to being treated in the hospital

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Smith and Campbell 2004[58] Scotland, UK Linked references: none Perspectives: health professionals	Aim: to explore how key health professionals view current models of outreach cancer care. (Study also collated data on current schemes serving remote rural cancer patients) Methodology: mixed methods (quantitative survey plus semistructured interview) Sampling: outreach clinics defined as more than 1 hour's drive from one of five cancer centres. Key agents were identified for interview (no further details)	Population: $n = 19$ Oncologists (5), clinical nursing manager (1), liaison sister (1), lead cancer nurse (1), specialist nurses (11) covering a total of 23 geographical locations of which seven did not provide chemotherapy Data collection: semistructured telephone interviews recorded and transcribed		Findings: Widely varying practices in the delivery of cancer care were reported. Health professionals felt the main issues are expertise, travelling, accessibility for patients, communication (between cancer centres and outreach clinics) and expansion of the rural service Professionals were generally keen to see an expansion of the rural services if expertise and communication issues could be addressed
Main reference: Stevens *et al.* 2004[56] Canada Linked references: Stevens *et al.*,[33] RCT; Breitfield,[104] editorial; Stevens *et al.*,[55] patient views Perspectives: health-care professionals	Aim: to explore the views and experiences of health-care professionals involved in a crossover RCT comparing home vs. outpatient chemotherapy for children Methodology: not clearly reported Sampling: purposive sampling to include range of experience, education and roles	Population: 33 health-care professionals were interviewed after 6 months of delivering the home chemotherapy programme Clinic nurses, community nurses, paediatrician, care co-ordinator, programme administrator, laboratory manager and pharmacist Data collection: individual semistructured interviews including topics on strengths and limitations of the programme, resource/training/ education implications, extending the programme, impact of the programme on their role Three experienced interviewers collected the data in a private room. All interviews recorded and transcribed	Mayring's content analysis was used. Transcriptions read line by line; memos used to record developing insights. Inductive reasoning used to organise data into categories and emergent themes Inter-rater checks carried out by independent researcher coding sections of transcripts; analysis discussed between two researchers to check for discrepancies and agree consensus NVivo used to display and manage the data including participant characteristics Thirteen broad categories developed then collapsed into three key categories	Perceived family benefits • Reduction in disruption • Decrease in psychological stress Human resources and service delivery implications • Consistency in personnel and care • Skills and knowledge requirements • Advantages of administering treatment at hospital • Problems with community laboratories • Communication problems • Uncertainty of the process • Need for eligibility criteria

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
			Data from community and hospital-based staff were initially analysed separately and then compared	Impact on role of health-care professionals: Hospital staff • Workload issues • Decreased patient interaction Community staff • Increased workload • Increased job satisfaction • Accommodating schedules
Main reference: Stevens *et al.* 2006[55] Canada Linked references: Stevens *et al.*,[56] Stevens *et al.*[33] Perspectives: patients (children) and parents	Aim: to examine the perspectives of children with cancer (and their parents) on a home chemotherapy programme Methodology: not reported Sampling: convenience sampling within a crossover RCT to recruit parents and children to the study following a 6-month period of home chemotherapy (some chemotherapy treatments had to be delivered in hospital; blood work took place in community laboratory)	Population: 23 families, of which five were single-mother families 24 individual parent and 14 individual child interviews took place Overall: 19 mothers, 5 fathers, and 14 children over 6 years took part. Average child age was 12 years Demographics reported in full paper Data collection: semistructured interviews asking about advantages and disadvantages of home chemotherapy, patient preference and how setting affected daily life were recorded and transcribed Place of interview was chosen by the participants and most took place in a private office in the hospital	Descriptive exploratory content analysis. Transcripts read line by line by two researchers. Memos created independently to record analytic insights, coding ideas and key points Data collected in a table according to common topics of discussion – using exact wording from participants Using inductive reasoning, data organised into categories that reflected emerging themes Compared raw data with themes to note similarities/differences and make comparisons Discussion and consensus was used to merge the categories from each researcher	Five main categories: 1. Financial and time costs 2. Disruptions to daily routines 3. Psychological and physical effects of home chemotherapy 4. Recommendations and caveats 5. Preference for home chemotherapy Conclusions: when home chemotherapy was compared with hospital clinic-based chemotherapy, parents reported fewer financial and time costs and less disruption to their work and family schedules, and children reported more time to play/study, improved school attendance, and engagement in normal activities. Although some parents felt more secure with hospital chemotherapy, most found it more exhausting and stressful. At home, children selected places for their treatment and some experienced fewer side effects. Although some co-ordination/communication problems existed, the majority of parents and children preferred home chemotherapy

General details	Aim/methodology	Population/data collection	Analysis	Summary of findings
Main reference: Taylor 2008,[24] Ph.D. thesis UK (England) Linked references: Taylor *et al.*,[110] full paper Perspectives: patients; carers; health-care professionals	Aim: to evaluate the perspectives of health-care professionals, patients and carers on ambulatory cancer care developments Methodology: mixed-methods approach using triangulation, underpinned by postmodern and social constructionist approaches Sampling: participants were identified through a mixture of convenience and purposive sampling	Population: Health-care users: Home chemotherapy users ($n = 3$) Nurse-/pharmacist-led clinic receiving capecitabine ($n = 3$) Chemotherapy day-unit users ($n = 3$) Carers ($n = 2$) Focus groups including patients and carers ($n = 2$ groups) Health-care professionals: Pharmacists; commercial home-care company; nurses (district and specialist); GPs; consultants; multidisciplinary group Data collection: focus groups and interviews conducted by the practitioner-researcher Most were recorded and transcribed, field notes taken during focus groups. Focus groups were conducted early on and used to develop the research	Thematic framework analysis: familiarisation; identification of thematic framework; indexing; charting and mapping; interpretation. Focus group data used to develop framework for analysis and structure the interviews	There was a continued drive by the government to move treatments from day-case hospital settings to outreach ambulatory care settings including cancer. Patients required flexibility throughout their journeys, hospital infrastructure and a collective experience with other patients. These could be lost through outreach ambulatory care developments. Health-care professionals identified a lack of professional and physical capacity to deliver ambulatory care as expressed in the policies

5-FU, 5-fluorouracil; MCU, mobile chemotherapy unit; QoL, quality of life; WHO, World Health Organization.

Appendix 9 NHS survey

This brief survey aims to collect a snapshot of current practice in the provision of home or community chemotherapy. There are a maximum of 28 brief questions to complete and we are very grateful for your participation.

The aim of this project is to synthesise existing research on the delivery of intravenous chemotherapy at home or in the community, and how it impacts on quality of life, safety, patient satisfaction and costs.

If you have any questions relating to the project or this survey please contact the research team by email: crd-home-chemo@york.ac.uk.

This project is funded by the NIHR Health Services and Delivery Research (HS&DR) Programme.

1. Contact details:

Name:

Job title or role:

Organisation:

Preferred contact email:

2. Are your patients able to have intravenous chemotherapy at home or in the community?

- Yes - at home or in the community
- No
- Not any more (service has been discontinued)
- I don't know

When home/community chemotherapy has never been available

3. Why is intravenous home/community chemotherapy not provided by your organisation?

4. Would your organisation consider offering intravenous home/community chemotherapy in the future?

- Yes
- Maybe
- No

When home/community chemotherapy is no longer available

5. Why has the provision of intravenous home/community chemotherapy been discontinued by your organisation?

6. Would your organisation consider offering intravenous home/community chemotherapy again in the future?

- ○ Yes
- ○ Maybe
- ○ No

Any particular reasons? _____

Unsure about provision

7. If you are not sure about provision of intravenous chemotherapy at home or in the community in your organisation, please suggest another person we could contact

_____

Service development

8. Were there any particular barriers or problems encountered when setting up the intravenous home/community chemotherapy service (clinical or organisational)?

_____

9. Was there a need for any training of existing staff, or the recruitment/training of new staff?

- ○ No
- ○ Yes (please give details)

10. Please select the type of intravenous chemotherapy your service provides below:

- ☐ We provide intravenous chemotherapy at home
- ☐ We provide intravenous chemotherapy in the community
- ☐ We provide intravenous chemotherapy in both settings

The following questions were presented if relevant to each of the settings where intravenous chemotherapy was provided:

11. When did your organisation start offering intravenous home/community chemotherapy?

_____

12. Is your intravenous home/community chemotherapy service provided internally or by a private provider?

- ○ NHS delivers all aspects of the service
- ○ Private provider delivers some/all of the service (please specify)

13. Thinking of the intravenous home/community chemotherapy service as a whole, please list all the team members who deliver it?
e.g. job title (number of staff)

14. How many nurses are involved in each intravenous home/community chemotherapy appointment?

15. Who prepares the cytotoxic drugs for the intravenous home/ community chemotherapy service?

- ☐ hospital pharmacy
- ☐ community pharmacy
- ☐ private pharmacy

Other (please specify)

16. How do patients interact with the service between treatments e.g. specialist phone line

17. What criteria are used to establish patient eligibility for the intravenous home/community chemotherapy service?

18. How are patients referred into the home/community chemotherapy service?

- ☐ Consultant
- ☐ Nurse specialist
- ☐ Other (please specify)

19. Approximately what proportion or percentage of those receiving intravenous chemotherapy are eligible for treatment at home/community?

20. Approximately what proportion or percentage of those offered intravenous chemotherapy at home/community take up the service?

Thank you

33. Is there anything else you would like to tell us in relation to the provision of intravenous home/community chemotherapy?

Appendix 10 Private survey

The aim of this project is to synthesise existing research on the delivery of intravenous chemotherapy at home or in the community, and how it impacts on quality of life, safety, patient satisfaction and costs.

This brief survey aims to collect a snapshot of current practice in the provision of home or community chemotherapy. There are a maximum of 7 questions to complete and we are very grateful for your participation.

If you have any questions relating to the project or this survey please contact us at crd-home-chemo@york.ac.uk.

This project is funded by the NIHR Health Services and Delivery Research (HS&DR) Programme.

1. Contact details:

Name:

Job title or role:

Organisation:

Email:

Phone number:

2. Does your organisation provide intravenous home and/or community chemotherapy funded by the NHS?

- Yes - we currently provide intravenous home chemotherapy service to the NHS
- Yes - we currently provide intravenous chemotherapy in a community setting to the NHS
- Yes - we provide intravenous home chemotherapy in both home and community settings to the NHS
- No - we do not currently provide this service, but have previously
- No - we have never provided this service

Current provision details

3. What aspects of home and/or community intravenous chemotherapy service does your organisation provide? (for example: cytotoxic drug preparation, nursing provision, etc.)

4. To which NHS organisations do you provide intravenous home and/or community chemotherapy?

5. Who is responsible for managing patient safety and adverse events and how are these monitored during the provision of home and/or community chemotherapy service(s) to the NHS?

Previous provision details

6. What aspects of home and/or community intravenous chemotherapy service did your organisation provide? (for example: cytotoxic drug preparation, nursing provision, etc.)

7. To which NHS organisations did you provide intravenous home and/or community chemotherapy?

8. Who was responsible for managing patient safety and adverse events and how were these monitored during the provision of home and/or community chemotherapy service(s) to the NHS?

Additional Information

We are interested in identifying any unpublished evidence to include in our systematic review and modelling. If you have any such evidence, please inform us on this page and we will contact you for further clarification.

9. Do you know of any unpublished evidence, such as: studies, audits, reports, patient satisfaction, or patient safety data?

- No
- Yes (please give details)

Thank you

Thank you for taking the time to complete this survey.

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RESEARCH ARTICLE Open Access

Randomised trials comparing different healthcare settings: an exploratory review of the impact of pre-trial preferences on participation, and discussion of other methodological challenges

Mark S. Corbett[1*], Judith Watson[2] and Alison Eastwood[1]

Abstract

Background: We recently published a systematic review of different healthcare settings (such as outpatient, community or home) for administering intravenous chemotherapy, and concluded that performing conventionally designed randomised trials was difficult. The main problems were achieving adequate trial accrual rates and recruiting a study population which adequately represented the target population of interest. These issues stemmed from the fact that potential participants may have had pre-trial perceptions about the trial settings they may be allocated; such preferences will sometimes be strong enough for patients to decline an invitation to participate in a trial. A patient preference trial design (in which patients can choose, or be randomised to, an intervention) may have obviated these recruitment issues, although none of the trials used such a design.

Methods: In order to gain a better understanding of the broader prevalence and extent of these preference issues (and any other methodological challenges), we undertook an exploratory review of settings trials in any area of healthcare treatment research. We searched The Cochrane Library and Google Scholar and used snowballing methods to identify trials comparing different healthcare settings.

Results: Trial accrual was affected by patient preferences for a setting in 15 of the 16 identified studies; birth setting trials were the most markedly affected, with between 68 % and 85 % of eligible women declining to participate specifically because of preference for a particular healthcare setting. Recruitment into substance abuse and chemotherapy setting studies was also notably affected by preferences. Only four trials used a preference design: the proportion of eligible patients choosing to participate via a preference group ranged from between 33 % and 67 %.

Conclusions: In trials of healthcare settings, accrual may be seriously affected by patient preferences. The use of trial designs which incorporate a preference component should therefore strongly be considered. When designing such trials, investigators should consider settings to be complex interventions, which are likely to have linked components which may be difficult to control for. Careful thought is also needed regarding the choice of comparator settings and the most appropriate outcome measures to be used.

Keywords: Healthcare settings, Service delivery, Patient preference, Preference trials, Randomised trial

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Background

Although it may seem self-evident that the physical environment of healthcare facilities has the potential to affect health outcomes, only quite recently has there been wide recognition that well-designed physical settings may play such an important role. Research evidence in this area (termed 'evidence-based design') has shown that the design of hospital physical environments may influence a range of patient health outcomes; staff outcomes; treatment durations; medication requirements; and may reduce patient, family and staff stress [1].

However, the effect of healthcare settings-the facilities where health interventions are delivered-may often not be evaluated. This may, in part, be due to deficiencies in knowledge and skills about how valid assessments should be performed, and also what should be evaluated [2]. In the UK, the NIHR (National Institute for Health Research) Health Services and Delivery Research (HS&DR) programme funds research to produce evidence on the quality, accessibility and organisation of health services, including evaluations of how the NHS might improve delivery of services [3]. This area of research covers the study of the effect of different healthcare treatment settings.

We (MC and AE) were part of a team which published a HS&DR-funded systematic review which evaluated the clinical- and cost-effectiveness of different healthcare settings for administering intravenous chemotherapy. We studied the effect of home, community, and outpatient settings on a range of outcomes, which were mostly patient-reported outcomes such as quality of life, preference, satisfaction and social functioning. From the trials identified in the systematic review it was apparent that performing randomised trials which compared settings was difficult, particularly in terms of achieving adequate trial accrual rates and recruiting a study population which adequately represented the target population of interest [4].

The inherent nature of settings as interventions means that potential participants may be likely to have pre-trial perceptions (opinions and likely preferences) about the trial settings they may be allocated. For example, some patients may feel anxious about the prospect of receiving treatment in a hospital setting and would rather be treated at home, while others may feel the hospital setting will provide safety and reassurance. These preferences will sometimes be strong enough for eligible patients to decline an invitation to participate in a trial. When performing randomised trials of most kinds of health intervention-though by no means all [5]- this particular type of recruitment problem seems unlikely to result in significant recruitment difficulties. This is because patients typically have little or no experience (real or vicarious) on which to form prior perceptions about at least one of the interventions being evaluated in the trial. It would therefore not be easy for patients to relate the potential benefits and harms of *all* the interventions due to be studied (and presented in a participant information sheet) to themselves as individuals. So, for many types of intervention, the presentation of information to prospective participants which explains the genuine uncertainty about which intervention might be best, should minimise non-participation rates due to preferences. However, the accrual data from the trials included in our chemotherapy setting systematic review suggested that this may not be the case for setting trials. Indeed, it is likely that some patients may decide not to participate *before* reading a participant information sheet.

In our systematic review of chemotherapy settings we concluded that the populations in many of the trials were likely to have been over-represented by hospital-averse (or home-inclined) patients, and under-represented by patients who were keen to receive hospital-based (outpatient) chemotherapy (since the outpatient setting was the only standard of care available to non-participants in nearly all of the trials). These self-selection bias and patient accrual problems appear difficult to overcome by using conventional randomised trial designs. A design which might address such problems is the patient preference trial, of which there are four major types: the Brewin and Bradley design, the comprehensive cohort, the Wennberg design and the Rucker design [5]. The comprehensive cohort design has been used where it is considered that patient preferences may introduce bias if conventional randomisation were to be used [6]. It essentially involves nesting an RCT within a larger observational cohort of patients: ambivalent patients are randomised, and patients with preferences receive their preferred intervention. All (consenting) patients are then followed up. Efficacy estimates would result from the randomised component of the study and any additional influence of motivational factors could be studied by comparing patients randomised to a particular setting with those who *chose* that same setting [7]. In our systematic review, none of the home chemotherapy trials incorporated a preference design.

Conventionally-designed randomised trials investigating the possible effect of a healthcare setting may therefore give rise to small cohorts of participants with results which have limited relevance, or generalisibility, to other populations (i.e. limited external validity), particularly when the combination of pre-trial preferences and subjective patient-reported outcomes arises. Furthermore, as intervention blinding (masking) is not possible in setting trials, patients randomised to their least-preferred option (often the standard care setting) may be more likely to withdraw from the trial, due to the disappointment of not being allocated the newer (or more appealing) setting. This kind of patient reaction to treatment allocation is

often termed resentful demoralisation [8]. In light of the findings in our systematic review, and in order to gain a better understanding of the prevalence and extent of these preference and recruitment issues, we undertook an exploratory review of settings trials in any area of healthcare treatment research. While examining these trials we also sought to identify any other setting-related methodological challenges which may be useful to document to help inform the planning and design of future trials. The importance of a consideration of the study designs used in this area of research is particularly relevant, given the call from NHS England's Chief Executive for changes in service delivery to be tested as rigorously as new treatments [9].

Methods

We began by searching The Cochrane Library and Google Scholar for relevant studies (or reviews which might include relevant studies). This review was exploratory and search terms were not pre-defined; searching was an evolving, iterative process which utilised search terms such as 'setting', 'home', 'community', 'home-based' and 'inpatient versus outpatient' (and vice versa). Snowballing methods-such as pursuing references of references and using Google Scholar's citation search facility-were then used to identify further studies. This has been shown to be a particularly efficient use of search time in reviews of complex evidence [10]. There were no date restrictions.

We included trials where a study objective was to compare the effects of different healthcare settings (i.e. the facilities where health interventions are delivered). For the assessment of the effect of preference on trial recruitment, randomised trials, or studies which consisted of both a randomised cohort and a cohort of patients who chose their treatments, were eligible. The randomisation-only trials had to report the numbers of eligible patients who opted not to be randomised, together with reasons for non-participation. Trials which did not meet these criteria were nevertheless examined for whether any other setting-related challenges with trial conduct were evident. For reasons of practicality, home exercise studies were only considered for cardiac rehabilitation interventions (since a large number of trials with interventions which incorporate home exercise exist). Studies which were stopped early due to recruitment difficulties were eligible.

Results

Effect of preferences on accrual and withdrawals for trials not offering a preference option

Table 1 lists the healthcare setting studies identified, with details on how preferences affected patient participation. In addition to intravenous chemotherapy, the clinical areas covered included: opioid dependence, alcohol abuse, cocaine abuse, giving birth, acute pulmonary embolism, deep vein thrombosis, and cardiac rehabilitation.

Trial recruitment was affected by patient preferences for a setting in 15 of the 16 identified studies. Birth setting trials were the most markedly affected, with between 68 % and 85 % of eligible women declining to participate specifically because of preference for a particular setting. Variation was evident across the intravenous chemotherapy trials with between 0 % and 38 % of eligible patients declining participation due to a setting preference. Recruitment into substance abuse studies was also notably affected by setting preferences with 67 % of opioid abusers, 33 % of alcohol abusers, and 33 % of cocaine abusers opting not to be randomised.

Two trials were stopped early: the OUTREACH trial was stopped due to poor accrual [11] and the Remonnay cross-over trial was stopped because 95 % of participants expressed a preference for home treatment [12]. The latter trial aimed to recruit 160 patients but was stopped when only 52 had been recruited; data from 10 patients who did not participate because they did not want home treatment were seemingly not considered when interpreting the 95 % preference result which triggered the trial to be stopped. It was also unclear how many patients were not invited to participate due to lack of physician consent (which was required as an inclusion criterion) [12]. Clinician views and preferences certainly had some impact on accrual in the OUTREACH trial; the trial authors stated that despite support from clinical colleagues at the trial design stage, in practice clinicians were reluctant to refer patients to the trial, with patient (and staff) safety being a key concern [11].

In contrast to the data on patient accrual into trials, the attrition of patients due to setting preferences did not generally appear to be a problem. Although the reporting of withdrawals was limited in several trials, only one trial reported notable numbers of post-randomisation withdrawals (11 %) for setting reasons [13].

Effect of preferences on accrual and withdrawals for trials using a preference design

Of the 16 healthcare settings studies identified, only four used a patient preference design in which patients could either opt for randomisation, or for their choice of setting (the shaded studies in Table 1) [14–17]. The proportion of eligible patients choosing to participate via a preference group ranged from between 33 % and 67 %. Some advantages of this study design are illustrated by comparing the two cardiac rehabilitation studies in Table 1: one used conventional randomisation alone [18] and one used a comprehensive cohort design [16]. Both trials were performed in England, recruiting around the same time (between 2002 and 2004 [18], and between 2000 and 2003 [16]). Although both studies *randomised*

Table 1 Effect of preferences on accrual and withdrawal in healthcare setting studies reporting reasons for non-participation

Trial and settings[a]	Number of potentially eligible patients	Number (%) not randomised			Target sample size	Number (%) randomised	Post-randomisation withdrawals which are, or could be, setting-related
		For setting-related preference reasons	Reasons not given or unclear	Other reasons			
Intravenous chemotherapy							
Borras[30] Home vs *outpatient*	88	0	1 (1)	0	NR	87 (99)	'Voluntary withdrawal': 1 home vs 6 outpatient
Corrie et al[10] (OUTREACH) Home vs local GP surgery vs *outpatient*	198[b]	53 (26.7): 35 (17) wanted hospital 16 (8) did not want GP surgery 2 (1) did not want home	35 (17.6)	13 (6.6)	390[c]	97 (48.9)	Limited details about the 23 withdrawals, though 'mainly due to disease progression'
King[12] (X) Home vs *outpatient*	87	7 (8): 4 (4.6) wanted hospital 3 (3.4) did not want home	0	6 (7)	NR	74 (85)	8 patients revoked consent for home setting after experiencing hospital setting
Remonnay[11] (X) Home vs *outpatient*	62	10 (16) did not want home	0	0	160[c]	52 (84)	None
Rischin[31] (X) *Home* vs *outpatient*	48[d]	7 (15) wanted home	12 (25) 'overlooked'	4 (8)	20	25 (52)	2 (one wanted only home setting and one wanted only hospital)
Stevens[32] (X) Home vs *outpatient*	50	19 (38): 16 (32) wanted hospital 3 (6) did not want home	2 (4)	0	22	29 (58)	2 children who started in the hospital group withdrew after commencing the study
Opioid dependence							
Gossop et al[17] Inpatient vs outpatient	60	40 (67) chose to participate via preference groups (group numbers not reported)	-	-	NR	20 (33)	NR
Place of birth							
Hendrix et al[33] *Home vs home-like outpatient*	116	79 (68)	34 (29)	2 (2)	500	1 (1)	NR (though only one 1 patient randomised)
Dowswell et al[34] (feasibility study) *Home vs outpatient*	71	60 (84.5): 47 (66.2) wanted home 13 (18.3)wanted hospital	0	0	NR	11 (15.5)	None
Byrne et al[35] *home-like outpatient vs outpatient*	863	662 (77): 343 (40) wanted home-like outpatient 319 (37) wanted outpatient	0	0	NR	201 (23)	1 transfer to birthing centre (following a request)
Alcohol abuse							
McKay 1995[15] *Inpatient vs*	288	96 (33) chose to participate via preference groups: 65 outpatient, 31 inpatient	0	144 (50)	NR	48 (17)	NR
outpatient							
Cocaine abuse							
McKay 1998[14] Inpatient vs outpatient	171	56 (33) chose to participate via preference groups: 37 (22) outpatient, 19 (11) inpatient	0	0	NR	115 (67)	NR, although inpatients had a significantly higher rate of treatment completion than outpatients
Acute pulmonary embolism							
Aujesky et al[36] *Inpatient vs* outpatient	470	85 (18): 61 (13) refused outpatient care 24 (5) refused inpatient care	14 (3)	27 (6)	320	344 (73)	2 inpatients withdrew consent
Deep vein thrombosis							
Levine et al[37] Home (LMWH) vs *inpatient (SH)*	739	135 (18): 128 (17) wanted admission to hospital 7 (1) did not want admission to hospital	0	104 (14)	500	500 (68)	None
Cardiac rehabilitation							
Dalal et al[16] *Home vs outpatient*	279 (1 site)	126 (45) chose to participate via preference groups: 72 (26) home, 54 (19) hospital	49 (18)	NR	104	104 (37)	Unclear
Jolly et al[18] Home *vs outpatient*	1207 (4 sites)	83 (7) wanted hospital	162 (13)	437 (36)	525	525 (43)	None

Key:
Grey-shaded studies used a patient preference design, all other studies used randomisation only
Numbers in brackets are % of the potentially eligible patients
[a]Italicised settings are those available outside of the trial (where information to assess this is reported)
[b]May be an underestimate of patients actually eligible as 'clinicians were reluctant to refer patients to the trial'
[c]Trials stopped early
[d]Patients 'registered in the chemotherapy in the home program'
(X) Cross-over trial
LMWH low-molecular-weight heparin (subcutaneous)
SH standard heparin (intravenous)

a similar proportion of eligible patients (around 40 %), the comprehensive cohort study recruited a further 45 % of eligible patients by giving them a choice of setting. The comprehensive cohort trial recruited 82 % of eligible patients compared with 43 % in the trial offering only randomisation. In the latter trial, 28 % of eligible patients 'did not wish to take part in a research study'. A further advantage of the comprehensive cohort design was the lack of self-selection bias: 7 % of eligible participants in the randomisation-only trial did not participate because they wanted the hospital setting, which was standard care [18]. It is possible that this trial may have had an inflated proportion of patients (at baseline) who preferred the home setting (since participating in the trial was the only way of receiving home treatment). However, in some areas of clinical research even the use of a preference trial may still not prevent the recruitment of a narrower population than desired. This was evidenced by the trial of rehabilitation in male alcoholics: half the eligible patients 'refused participation in research' [15].

Other methodological challenges associated with setting studies

Our exploratory review also found evidence suggesting that the following issues should be considered when planning a setting study.

Choice of outcome measures

The choice of outcome assessment measures to be used may warrant additional thought (beyond the considerations

needed when evaluating conventional healthcare interventions). Some of the outcome measures available to investigators studying healthcare settings may have only been used previously to evaluate therapeutic interventions, and may therefore not be sensitive enough to detect the benefits associated with a setting. For example, across the home chemotherapy trials, the available quality of life tools tended to focus heavily on physical functioning, rather than on issues such as the time and energy available to patients [4].

Other key outcomes which are often evaluated in setting trials are patient satisfaction and patient preference (i.e. *post*-trial preference). Assessing satisfaction with childbirth settings has been reported as being difficult; satisfaction is determined by a wide variety of factors, so reducing it to a single ordinal outcome may be meaningless [19]. Depending on the study in question, decisions will therefore need to be made on the trade-off between the speed and simplicity of using a single-item measure, and the useful detail provided by more time-consuming multi-item questionnaires [20]. Where patient preference is deemed an important outcome, a study design with a cross-over component should be considered-wherever feasible-since each patient should (theoretically) experience both settings. However, cross-over designs should only really be used for studying patients with relatively stable disease states. Although preferences were studied in many of the home chemotherapy cross-over trials, only one trial investigated *strength* of preference, which proved to be an important assessment: around a third of patients changed their setting preference when they were told their preferred setting was to involve an extra hour of waiting [13]. Results from trials which do not consider strength of preference may therefore have limited use. With these examples in mind, the collection of qualitative patient data should strongly be considered to help evaluate the full range of benefits that different settings may offer. Qualitative data generated from interviews with patients and healthcare professionals before and after a trial can also provide valuable insight regarding barriers to recruitment as well as patients' healthcare priorities [11].

Consideration of settings as complex interventions

Complex interventions are characterised according to several criteria including the number of interacting components, the number and difficulty of behaviours required by those delivering or receiving the intervention, and the degree of intervention flexibility or tailoring permitted [21]. Organisational and care parameters are very likely to form important intervention components when settings are studied. The individual effects of the different, yet interacting components of a setting intervention can be difficult to elucidate. It is therefore likely that most healthcare settings should be considered complex interventions when being evaluated in a trial.

This complexity could make evaluation of any 'setting effect' problematic: some investigators may even need to consider whether attempting to study the setting will be viable at all. The following example illustrates how different staff attitudes across settings can have implications for the conduct and results of a trial. An RCT of inpatient versus outpatient opioid detoxification was undertaken because previous trials had methodological limitations-the key one being that different medication regimens had been used in each setting, so the opportunity to study the impact of setting on the likelihood of success had been missed [22]. The newer trial therefore aimed to administer the same medical treatment regimen, for the same period, in an inpatient and an outpatient setting. The same clinical protocol was used for inpatient and outpatient staff, although all staff were given some flexibility in administering the protocol (clinicians could increase the period of full-dose lofexidine by up to 7 days, if clinically indicated). However, at the end of the trial, the outpatient group had received a significantly longer mean medicated period than the inpatient group (17.9 days versus 11.2 days) which was linked to the greater flexibility applied by the outpatient staff. Furthermore, although the protocol required clinicians to terminate the detoxification if a patient tested positive for opioids, cocaine, amphetamine, or unprescribed benzodiazepines, no guidance was provided for cannabis. This led to an unanticipated difference in practice with outpatient nurses routinely ignoring positive cannabis test results, and inpatient staff adopting a strict zero-tolerance approach to all illicit drugs. Other medication differences may have arisen due to the fact that inpatients were supervised in taking all of their medication whereas outpatients were not. Although attempts to control for possible confounders are commendable, this examples suggests this approach should nevertheless be tempered by an acceptance that setting interventions have multiple components which may be inherently linked and may be difficult to control for.

Choice of comparator settings

Another issue to consider when designing a setting trial is how 'standard' or 'usual' the usual care setting is and how likely it is to vary across study sites. New healthcare settings should only be trialled in locations where there appears to be a need. The relevance of this issue was exemplified in a trial of intermediate care clinics for diabetes (ICCD, which are community-based) which were compared with usual GP care (with referral to secondary care as required) [23]. This was a cluster randomised trial (randomising 49 GP practices) performed across three English primary care trusts. The trial had

recruitment problems, with GPs not referring enough patients: only 16 % of those eligible were recruited. One of the reasons for this was the variation in the amount of referrals made by practices and professionals. Those making a higher number of referrals tended to view intermediate care clinics as a higher level of care, while those making few referrals were usually from practices with significant diabetes expertise and skills and were therefore less likely to regard intermediate care as offering more than could be offered in-house [24].

Discussion

The results from our exploratory review suggest that, in trials of healthcare settings, accrual may be seriously affected by patient preferences. The use of trial designs which incorporate a preference component should be more widely adopted when settings are being trialled, since results from conventional RCTs may have very limited applicability to wider patient populations. There may also be important consequences of the small sample sizes which often result from conventional RCTs: trials showing no effect may simply be underpowered to detect effects which might truly exist, or trials with statistically significant results may in fact be reporting chance effects. Investigators planning a trial in this area of research may also need to view the settings as complex interventions which have linked components which may be difficult to control for. Careful consideration may also be needed regarding decisions on which comparator settings and outcome assessment measures might be most appropriate.

The results of a systematic review of preference trials across a broad range of interventions have indicated that although preference groups can sometimes yield different results to randomised groups, self-selected patients do often have similar outcomes to randomised patients [6]. However, those differences in results which were seen in trials in this review were more frequently found to be significant in the smaller studies; this finding is important for our exploratory review since 10 of the 16 studies in Table 1 randomised fewer than 100 patients. Where findings indicate no differences between randomised and preference cohorts, it should also be considered that this may be a reflection of patients choosing a particular treatment for reasons *other* than believing it will be the most effective (in terms of improvements in key trial outcomes). For example, alcohol abusers may prefer inpatient treatment because they want a safe, comfortable place to stay, or they may prefer outpatient treatment as it may not interfere as much with their daily routines [15]. So, effects on patient-perceived quality of life (such as improved relationships, self-awareness and activities of daily living) may be more important to some patients than the effect on the alcohol and drug related outcomes important to the trial investigator [25].

In our exploratory review very limited data were available on *why* patients had preferences which resulted in the offer of participation being declined. One identified study (not tabulated due to the limited detail on reasons for non-participation) did nevertheless highlight that travel issues may adversely affect recruitment. It was an RCT of inpatient versus outpatient chronic pain management; a post-hoc analysis study, which focussed on the effects of patient preference, found that the high rates of refusal to be randomised resulted from the difficulty in traveling from home to hospital. Travel was more demanding for outpatients (in time and costs) than for inpatients. Recruitment was also affected by an unanticipated predominance of patients referred from distant locations; patients living further from the treatment unit were found to be less likely to agree to randomisation [26].

The common theme linking all the methodological issues discussed in our exploratory review is their potential to affect the external validity of trial results. External validity, also sometimes referred to as applicability or generalisability, is the extent to which a result can be reasonably likely to be replicated when applied to a definable group of patients in a particular clinical setting. Lack of external validity is a common criticism by clinicians of RCTs, systematic reviews and guidelines. However, quantification of external validity can be difficult, requiring clinical rather than statistical expertise and a detailed understanding of the particular clinical condition under study and its management in routine clinical practice [27–29]. Assessments of external validity can prove particularly difficult when the information needed is either poorly defined or not reported. The requirement for providing sufficient details on intervention protocols may be especially important as complex interventions may work best if tailored to local circumstances, rather than being completely standardised; clarity in the reporting of how much change or adaptation is permissible is therefore desirable [21]. Both the complexity of the components of setting interventions, and the variability in how patients are recruited (which ultimately causes variability in *who* is recruited) has implications for how practicable it may be for the trialled interventions to be replicated by other organisations.

Implications for future studies

It appears likely that most of the RCTs identified in our study would have benefitted from using a preference design, although it was unclear why so few of the studies actually gave patients the option of choosing their setting. Perhaps it was due to a lack of knowledge of the existence of such designs, or a fear of straying from the RCT gold standard; the use of less well-known designs

may lead to difficulties when acquiring funding, or approvals from ethics or other regulatory committees. Our hope is that in the future, both setting trialists and funders might consider different, arguably more appropriate, methodological approaches than those offered by conventional randomised trial designs. Regardless of the study methods used by investigators, the importance of performing feasibility studies in this area of research cannot be over-stated. Furthermore, any subsequent larger studies should begin with a pilot phase.

In addition to potentially offering improved trial accrual and external validity, patient preference trials may produce more useful estimates of likely rates of uptake of the different settings to help inform future service provision. They may also provide enough data to more clearly identify any setting-related safety issues (which appeared to be one of the key clinician concerns about the implementation of a home or community chemotherapy service [11]). Larger studies might also enable useful assessments to be made of whether setting-related issues which are important to patients vary according to patient characteristics. For example, for patients receiving chemotherapy, waiting times may be more important for patients who are working, whereas transport issues may be more important for elderly patients.

Limitations

Being exploratory, our review does have limitations. The purpose of the study was to identify challenges and issues which may sometimes be encountered in setting trials in order that they might be minimised in future trials. We did not aim to comprehensively and systematically identify all setting trials, and accept that some relevant studies will not have been identified. Nevertheless, a strength of this study is that we did consider studies from any type of clinical setting in order to try and detect a range of methodological issues. Disappointingly, but perhaps unsurprisingly, our assessment of the impact of preferences on trial recruitment was constrained by the limited reporting of what happened to patients before they were randomised. Many trials did not report adequate details on eligible patients who were not randomised, which limited the number of trials available to us for studying the recruitment outcomes reported in Table 1. Although the CONSORT guidelines (for reporting parallel-group randomised trials) state that the number of patients assessed for eligibility should be reported, it makes little reference of the numbers of eligible patients who were not randomised, and suggests that measures of external validity are arguably less important than the other flow diagram counts [30]. We think that in this area of study the reporting of data to inform external validity is very important. The lack of such data in trial reports may not necessarily be due to limited reporting, but might instead be due to poor trial data acquisition and collation methods.

Conclusions

In trials of healthcare settings, accrual may be seriously affected by patient preferences. The use of trial designs which incorporate a preference component should therefore strongly be considered. Investigators should consider the implications of the fact that many settings are likely to be complex interventions, which have linked components which may be difficult to control for. When planning setting trials, careful thought is also needed regarding the choice of comparator settings and the most appropriate outcome assessment measures to be used.

Abbreviations

CONSORT: Consolidated standards of reporting trials; GP: General practitioner; HS&DR: Health services and delivery research; ICCD: Intermediate care clinics for diabetes; NHS: National health service; RCT: Randomized controlled trial

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Authors' contributions

MC conceived the study, developed its design and coordination, identified studies, extracted and analysed the data, drafted the manuscript and coordinated the authors' comments. JW contributed to the interpretation of data, and helped to revise the manuscript. AE participated in the design of the study, contributed to the interpretation of data, and helped to revise the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

1. Ulrich RS, Zimring C, Zhu XM, DuBose J, Seo HB, Choi YS, et al. A Review of the Research Literature on Evidence-Based Healthcare Design. Herd-Health Env Res. 2008;1(3):61–125.
2. Elf M, Frost P, Lindahl G, Wijk H. Shared decision making in designing new healthcare environments-time to begin improving quality. BMC Health Serv Res. 2015;15. doi:10.1186/s12913-015-0782-7.
3. The NIHR Health Services and Delivery Research (HS&DR) Programme. Applying for research funding. Southampton: HS&DR Programme, National Institue for Health Research. 2013.

4. Corbett M, Heirs M, Rose M, Smith A, Stirk L, Richardson G, et al. The delivery of chemotherapy at home: an evidence synthesis. Health Serv Deliv Res. 2015;3(14):1–182.
5. Kowalski CJ, Mrdjenovich AJ. Patient preference clinical trials: why and when they will sometimes be preferred. Perspect Biol Med. 2013;56(1):18–35. doi:10.1353/pbm.2013.0004.
6. King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, et al. Impact of participant and physician intervention preferences on randomized trials. A systematic review. JAMA. 2005;293(9):1089–99.
7. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. BMJ. 1989;299(6694):313–5. doi:10.1136/bmj.a1864.
8. Bradley C. Designing Medical and Educational Intervention Studies-a Review of Some Alternatives to Conventional Randomized Controlled Trials. Diabetes Care. 1993;16(2):509–18.
9. Moberly T. Service redesign should be tested as rigorously as new treatments, NHS chief says. BMJ. 2014;348:g3744.
10. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ (Clinical research ed). 2005;331(7524):1064–5.
11. Corrie PG, Moody AM, Armstrong G, Nolasco S, Lao-Sirieix S, Bavister L, et al. Is community treatment best? A randomised trial comparing delivery of cancer treatment in the hospital, home and GP surgery. Br J Cancer. 2013;109(6):1549–55. doi:10.1038/bjc.2013.414.
12. Remonnay R, Devaux Y, Chauvin F, Dubost E, Carrere MO. Economic evaluation of antineoplastic chemotherapy administered at home or in hospitals. Int J Technol Assess Health Care. 2002;18(3):508–19.
13. King MT, Hall J, Caleo S, Gurney HP, Harnett PR. Home or hospital? An evaluation of the costs, preferences, and outcomes of domiciliary chemotherapy. Int J Health Serv. 2000;30(3):557–79. doi:10.2190/CY03-EV15-K38Y-X4AA.
14. McKay JR, Alterman AI, McLellan AT, Boardman CR, Mulvaney FD, O'Brien CP. Random versus nonrandom assignment in the evaluation of treatment for cocaine abusers. J Consult Clin Psychol. 1998;66(4):697–701.
15. McKay JR, Alterman AI, McLellan AT, Snider EC, O'Brien CP. Effect of random versus nonrandom assignment in a comparison of inpatient and day hospital rehabilitation for male alcoholics. J Consult Clin Psychol. 1995;63(1):70–8.
16. Dalal HM, Evans PH, Campbell JL, Taylor RS, Watt A, Read KL, et al. Home-based versus hospital-based rehabilitation after myocardial infarction: a randomized trial with preference arms-Cornwall Heart Attack Rehabilitation Management Study (CHARMS). Int J Cardiol. 2007;119(2):202–11. doi:10.1016/j.ijcard.2006.11.018.
17. Gossop M, Johns A, Green L. Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. BMJ. 1986;293:103–4. doi:10.1136/bmj.293.6539.103.
18. Jolly K, Taylor R, Lip G, Greenfield S, Raftery J, Mant J, et al. The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Home-based compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence. Health Technol Assess. 2007;11(35):1–118.
19. Hundley VA, Milne JM, Glazener CMA, Mollison J. Satisfaction and the three C's: continuity, choice and control. Women's views from a randomised controlled trial of midwife-led care. BJOG. 1997;104(11):1273–80. doi:10.1111/j.1471-0528.1997.tb10974.x.
20. Speight J. Assessing patient satisfaction: Concepts, applications, and measurement. Value Health. 2005;8:S6–8. doi:10.1111/j.1524-4733.2005.00071.x.
21. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337(7676). doi: 10.1136/bmj.a1655.
22. Day E, Strang J. Outpatient versus inpatient opioid detoxification: a randomized controlled trial. J Subst Abuse Treat. 2011;40(1):56–66. doi:10.1016/j.jsat.2010.08.007.
23. Wilson A, O'Hare JP, Hardy A, Raymond N, Szczepura A, Crossman R, et al. Evaluation of the clinical and cost effectiveness of intermediate care clinics for diabetes (ICCD): a multicentre cluster randomised controlled trial. PLoS One. 2014;9(4), e93964. doi:10.1371/journal.pone.0093964.
24. Wilson A, Hardy A, Armstrong N, Baines D, Baker R, Crossman R, et al. A cluster randomised controlled trial of the effectiveness and cost-effectiveness of intermediate care clinics for diabetes (ICCD). Final report. NIHR Service Delivery and Organisation programme: Southampton; 2013.
25. Thurgood S, Crosby H, Raistrick D, Tober G. Service user, family and friends' views on the meaning of a 'good outcome' of treatment for an addiction problem. Drug-Educ Prev Polic. 2014;21(4):324–32. doi:10.3109/09687637.2014.899987.
26. de C Williams DC, Nicholas MK, Richardson PH, Pither CE, Fernandes J. Generalizing from a controlled trial: the effects of patient preference versus randomization on the outcome of inpatient versus outpatient chronic pain management. Pain. 1993;83:57–65.
27. Rothwell PM. Commentary: External validity of results of randomized trials: disentangling a complex concept. Int J Epidemiol. 2010;39(1):94–6. doi:10.1093/ije/dyp305.
28. Burchett H, Umoquit M, Dobrow M. How do we know when research from one setting can be useful in another? A review of external validity, applicability and transferability frameworks. J Health Serv Res Policy. 2011;16(4):238–44. doi:10.1258/jhsrp.2011.010124.
29. Green LW, Glasgow RE. Evaluating the relevance, generalization, and applicability of research-Issues in external validation and translation methodology. Eval Health Prof. 2006;29(1):126–53. doi:10.1177/0163278705284445.
30. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:869. doi:10.1136/bmj.c869.