Rethinking ADHD intervention trials: the feasibility testing of two treatments and a methodology.

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Abstract

Background

Attention deficit hyperactivity disorder (ADHD) is a leading cause of child referrals to mental health services, and major risk factor for early criminality, school drop-out and exclusion. It imposes significant burdens on children, their families and a wide range of public services.

Long-term evidence for the effectiveness of main and non-mainstream treatments is weak. Current approaches to generating evidence are expensive and slow. New approaches are required to identify treatments which can improve outcomes. This thesis rethinks the identification and testing of interventions to improve outcomes for ADHD.

Methods.

Using the Trials within Cohorts (TwiCs) approach, the Sheffield Treatments for ADHD Research (STAR) project recruited a cohort of children with ADHD and collected outcomes at 0, 6 & 12 months from carers and teachers. For the first randomised, controlled trial (RCT) embedded in the cohort an eligible proportion were randomly selected and offered treatment by homeopaths, or nutritional therapists, additional to usual care. At 6 months, their outcomes (Conners Global ADHD Index) were compared with those not offered interventions, and the feasibility of the methods and interventions assessed.

Results

Between September 2015/2016, the target number of 144 participants were recruited to the cohort. 124 were eligible for the 1st trial and randomised. 83 were offered a treatment of which 72 accepted and 50 attended 1+ appointments. 89/124 paired (baseline & 6-months) carer and 31/100 paired teacher questionnaires were available for analysis. Teachers' responses were too few, and unstable, but there were preliminary indications of treatments' effectiveness according to carers: t = 1.08, p= .28 (-1.48, 4.81) SMD .425 for treatment by homeopaths; t = 1.71, p = .09 (-.347, 5.89), SMD = .388 for treatment by nutritional therapists. No serious adverse events attributable to treatments were reported.

The TwiCs approach was feasible but required some modifications. Return of carer questionnaires was improved by addition of an incentive. Delivery of treatments was feasible, but attendance rates affected by therapists' contacting strategies, and one therapist dropped out.

Discussion

A representative cohort was quickly recruited, and the first pilot RCT efficiently conducted. Attrition and uptake were comparable with other pragmatic studies in ADHD. Although therapists reported that delivery was challenging, 70% of participants accepting treatment received at least three consultations and reported they were helpful. No serious adverse events attributable to treatment occurred.

Modifications are required to improve poor return of teacher outcomes, therapist's contacting strategies, crossover from treatment to usual care (40%), and cohort representativeness.

Conclusion

The TwiCs design can make an important contribution in the search to improve outcomes for those with ADHD. The STAR project demonstrated the feasibility of the TwiCs approach to pragmatic RCT design for testing interventions for children with ADHD. In the pilot RCT the novel interventions showed preliminary indications of effectiveness according to carers.

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Glossary.

ADHD – *Attention Deficit Hyperactivity Disorder*

ASCs – *Autism Spectrum Conditions*

CAM – *Complementary and Alternative medicine.*

CGI - *Conner's Global Index*

CPRS – *Conner's Parent Rating Scale*

cm RCT – *Cohort multiple Randomised Controlled Trial*

DSM - *Diagnostic and Statistical Manual (of Mental Disorders)*

Hom – *treatment by a homeopath*

MTA - *Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder*

MYMOP – *Measure Your Own Medical Outcome Profile*

NICE – *National Institute for Clinical Excellence*

NT – *treatment by a nutritional therapist*

QALY - *The quality-adjusted life year*

SNAP – *Swanson, Nolan & Pelham questionnaire*

TAU – *treatment as usual*

TwiCs – *Trials within Cohorts*

Chapter 1 Introduction

1.1 An overview of the thesis

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed and treated childhood psychiatric disorders. Children with ADHD are hyperactive (fidgety and unable to sit still for long periods), and impulsive (doing things without stopping to think). They find it hard to concentrate and follow instructions, which is a particular problem at school, and to regulate their emotions, which is a problem at home, with their peers, and gets them into trouble.

ADHD type behaviours have been described in medical literature for over 100 years (Reimherr, 2005). Heterogeneity (non-uniformity) is a feature of ADHD expression and children often have a wide range of other diagnoses and co-occurring problems such as Autism Spectrum Conditions (ASCs), Conduct Disorders, sleep disorders, tics, gut dysbiosis, reading and other learning problems. A diverse range of risk factors are suggested in the literature including environmental exposures in utero, birth trauma, parental stress, and genetic susceptibility.

Treating the condition is challenging. Many do not consider the condition to be curable, so interventions are offered to help to manage symptoms. The two types of interventions offered by the NHS, recommended by NICE (2008), are behaviour change programmes and pharmaceutical medications. Pharmaceutical medications are associated with common side effects, and tend to be discontinued, particularly by teenagers. They may not be effective over the long-term, or for up to 25% of the population, especially those with co-occurring autism. Behaviour change programmes, the first line of intervention offered in the UK for those with moderate ADHD, are costly, not universally available, considered less effective than pharmaceutical interventions at reducing core ADHD symptoms, and effects may not be sustained once programmes end. Neither intervention appears to be influencing the long-term negative outcomes associated with the condition.

Interpreting and comparing the evidence, particularly the long-term evidence, for the effectiveness of these two types of interventions is difficult for several reasons. Comparison is difficult largely because trials of drugs tend to be explanatory whereas trials of behaviour change programmes tend to be pragmatic. Trials were originally identified as being either explanatory or pragmatic by Schwartz and Lellouch (1967). Explanatory trials aim to evaluate the efficacy of an intervention in a well-defined and controlled setting, in comparison to a placebo or another intervention. Pragmatic trials aim to test the effectiveness of an intervention in broad routine clinical practice and measure “the extent to which a specific intervention…. when deployed in the field in routine circumstances does what it is intended to

do for a specific population" (Last, Spasoff, & Harris, 2001). This means the two types of trials are more/less tightly controlled, have more/less potential for bias, higher/lower expected effect sizes, and address different research questions.

It is difficult to assess the ability of the two types of intervention to improve long-term outcomes, because despite many RCTs having been conducted the majority are short-term. It is unclear whether the lack of evidence found in the few long-term studies conducted is due to adherence and acceptability issues or the lack of effectiveness of the interventions. Evidence from short-term trials is used to make long-term treatment decisions.

Current approaches to generating evidence are expensive and slow, and new approaches are required to identify treatments which can improve outcomes particularly in the long-term. Not only do ADHD trials tend to be of short duration, but interventions are trialled one at a time, which is costly in terms of time and resources. Each trial recruits its own standalone population and often fail to recruit sufficient participants (McDonald, et al., 2006) (Sully, Julious, & Nicholl, 2013). At the trial end, the trial population is disbanded, and for the next trial a new RCT is designed and new trial population recruited. Trials use different comparators, have different aims, and often have tight inclusion and exclusion criteria, so it is difficult to be confident that results pertain to all those with ADHD which is associated with co-morbidities that are often exclusion criteria.

Good quality evidence for interventions to improve long-term outcomes is needed. Not only do we need more long-term studies of the effectiveness of mainstream interventions, but novel treatments need to be trialled to see whether they might address treatment gaps, and the way that research is conducted needs re-thinking to address some of the issues described above. This thesis rethinks the methods for creating evidence to assess the effectiveness of treatments for ADHD to improve long-term outcomes. It takes a novel approach to trialling interventions, trials two novel interventions, and asks: "is the Trials within Cohorts (TwiCs) design feasible to generate evidence about the effectiveness of interventions for ADHD?", by pilot testing the effectiveness of the novel treatments using the TwiCs approach (Relton, O'Cathain, Nicholl, & Torgerson, 2010).

The TwiCs design, also known as the cohort, multiple randomised controlled trial (cmRCT) design, is a new approach for testing interventions and improving outcomes. First a large observational cohort of patients with the condition of interest is recruited and their outcomes regularly measured. Then for each randomised controlled trial, information from the cohort is used to identify eligible participants. Some eligible cohort participants are randomly selected and offered the trial intervention(s) additional to their usual care. The outcomes of the randomly selected groups are then compared with the outcomes of those eligible participants not selected and continuing with their usual care.

The design allows the comparative effectiveness testing of multiple interventions in a representative population over the long-term. It enables accurate comparison of different types of intervention, since validity, population, comparator and outcomes are held constant for all interventions tested. It tests whether important, objective outcomes are improved over the long-term.

The acceptability of interventions is tested, providing useful information about how acceptable they might be in practice. It uses an approach to informed consent whereby information about interventions is provided only to the intervention group(s) after randomisation, aiding speedy recruitment of sufficient numbers (Viksveen, Relton, & Nicholl, 2017).

The design is efficient and cost-effective because it provides a facility for multiple trials to be run, with economies of scale. Unequal randomisation can be used, reducing costs associated with treatments (Viksveen, Relton, & Nicholl, 2017). Once a cohort is in place, trials can be quickly and cheaply conducted, and there is reduced risk of trials run within existing cohorts failing to recruit.

Running trials of both main and non-mainstream interventions using the TwiCs design can contribute to the evidence base regarding the potential of current and novel interventions to improve long-term outcomes for those with ADHD.

1.2 Reflexivity and bias.

Bias is a term used to describe a tendency towards a particular perspective. In conducting clinical research, researchers are urged to be upfront, explicit and transparent about their motivations for carrying out the research (Jadad & Enkin, 2007). Reflexivity refers to sensitivity to the ways in which researchers may shape the research process, and it is suggested researchers should make any personal and intellectual biases plain at the outset (Mays & Pope, 2000). This section therefore addresses concerns about bias by taking a reflexive approach and describing my biography, beliefs and agenda as they relate to the research undertaken in this thesis. I have endeavoured to make plain my personal viewpoints and experiences which may affect my research.

1.2.1 My background

My primary training and career were in education. After completing a B.Ed. in English Literature and Education at Cambridge University, I worked as a teacher (including with those with special educational needs), and parent educator within Sure Start, until my own four children were born. One formative post in St George's Hospital psychiatric unit as a member of a team working with school refusing children, highlighted the difficulties in making tangible differences to these children's lives.

When my children were small, I trained as a homeopath with a view to managing their first aid needs. My great aunt was a medically trained doctor and homeopath and I had been brought up using homeopathic remedies to manage our health. Whilst training, and under supervision, I provided homeopathic treatment to a nine-year-old child (consisting of three consultations over 18 weeks and individually tailored homeopathic remedies). The child had a diagnosis of ADHD, nocturnal enuresis, history of attempted suicide, multiple warts, was illiterate, and had destroyed much of the family home. These symptoms and behaviours gradually disappeared over the homeopathic treatment period, during which time he learnt to read. This was a pivotal experience since it appeared to me that the child had experienced greater improvements with treatment than anything I had previously provided in the classroom or as a parent educator.

I wondered whether the improvement might be due to the homeopathic treatment, or to other factors. I wondered if homeopathic treatment might be generally effective for children with ADHD, and what the evidence was for homeopathic treatment for ADHD? I continued to treat children with ADHD, but when I suggested homeopathic treatment to schools and educators, the usual response was scepticism and rebuttal. This led me to wonder whether there was a problem with the evidence base. My experience with this child and subsequently with others has led me to explore systematically whether homeopathic treatment is helpful for these children, what kind of evidence is needed to ascertain this and for this treatment to be considered as an option.

To start answering some of my questions I undertook a BSc in Homeopathy at Thames Valley University. For the research module I conducted a literature review of the trials of homeopathy for ADHD. I then undertook a consecutive case series, whereby I recruited 20 children with a diagnosis of ADHD to receive a year's homeopathic treatment from myself, and their outcomes were documented. This received funding from Turner's Court Youth Trust (an ex borstal supporting measures to prevent imprisonment) and matched funding from the Homeopathic Research Institute. The children appeared to benefit from the treatment, but I understood that more robust research methods were needed.

Whilst implementing the case series, I undertook an MSc in Research Methodology in Psychology at Goldsmiths, University of London. At the suggestion of my tutors, having recruited 20 children to the treatment group, I then recruited a further 10 children as a control group. They received similar time and attention from myself but no homeopathic treatment. Carers of the children receiving homeopathic treatment reported statistically significant improvements compared to those receiving similar time and attention (section 4.3) (Fibert, Relton, Heirs, & Bowden, 2016). But I again realised that more rigorous research, using randomisation, would be required for the results to be considered robust.

Parallel to this academic and clinical exploration, ADHD has had a personal impact on my family, with most of my husband's family and two of my four daughters receiving a diagnosis of ADHD. One of my daughters initially managed her ADHD with Ritalin to help her complete her undergraduate degree, but disliked how it made her feel and now manages it through a gluten and dairy free diet, nutritional supplementation and lifestyle. The other daughter did not experience improvements with either Ritalin or Atomoxetine (non-methylphenidate based medication), undertook a course of CBT therapy, and is helped by anti-depressants. Both receive occasional homeopathic treatment. This has provided me with an intimate experience of the impact of diagnosis, management, pharmaceutical medication, behavioural programmes, nutritional supplementation, dietary changes and homeopathic treatment.

1.2.2 The implications of my experience

My viewpoint that homeopathic treatment is helpful for children with ADHD has been influenced by my biography, my academic, and my professional training. My varied career path as a teacher, parent educator, carer, homeopath and researcher has had a common thread, in being consistently motivated by a desire to improve outcomes for struggling children, and I have explored different careers with this aim in mind.

I bring an in-depth understanding of ADHD and the interventions trialled from a constructionist viewpoint, which contributes positively to the research process (Postholm & Madsen, 2006). However, there is the potential for bias in that I may be tempted to seek confirmation for my clinical, educational, familial and informal observations. For example, I believe I have observed multiple instances whereby homeopathic treatment and nutritional interventions have facilitated improvements, but these improvements could have been due to other factors. Therefore objectivity, transparency and reflexivity have been required at all stages of the research process to minimise the potential impact of this view.

Steps taken to reduce risk of bias include the independent procedures of ethical review, independent scientific review, and University of Sheffield research governance systems, which scrutinised all stages of the research process. The study was overseen by a steering committee of independent academics, researchers and clinicians. The randomisation process was performed by independent researchers, and the trial protocol was published prior to trial start (http://www.isrctn.com/ISRCTN17723526). Study data are fully reported, and supervision provided by academics from diverse disciplines (public health, statistics, health economics and psychology) with differing opinions on the interventions tested.

1.2.3 Epistemology

For this PhD I have conducted empirical research, with the understanding that such knowledge is prioritised by decision makers, who value the primacy of the RCT as a method of establishing a causal link between intervention and outcome (Medical Research Council (MRC), 2000). However, other forms of knowledge have also been used. Anecdotal knowledge informed my initial research hypothesis, and authoritative knowledge was used when reviewing the professional literature. Logical knowledge was used outlining the research problem to be addressed, interpreting the evidence base, and reasoning from findings to conclusions.

1.2.4 Ontology

I have taken an essentially positivist, pragmatic perspective in conducting the empirical research described in this thesis. However, I consider both interpretivist and empirical approaches are used in order to answer "real-world" research questions (Feilzer, 2010). I think that it is likely that empirical research into novel interventions is assessed through interpretivist lenses, and that interpretation of such studies will be affected by individual knowledge, experience and belief. Therefore transparent understanding of the ontological perspectives of others, as well as my own can increase clarity.

1.3 Aims and Objectives of the thesis

This thesis addresses the question: "is the Trials within Cohorts (TwiCs) design feasible to generate evidence about the effectiveness of interventions for ADHD?",

The aim of this thesis is to assess the feasibility of the TwiCs design to provide information to enable the evaluation of treatments for ADHD.

The objectives of this thesis are to:

- describe ADHD, its impact across services, the range and effectiveness of mainstream interventions, gaps in provision, and key issues
- identify key stakeholder requirements to assess acceptability, clinical and cost effectiveness of treatments
- identify a range of novel treatments for ADHD that are being used which have some evidence for their effectiveness and select two to be tested
- describe and review the evidence for these two selected treatments for ADHD: treatment by homeopaths and treatment by nutritional therapists
- explore the key issues regarding trial designs for these interventions

- assess the feasibility, acceptability, deliverability, safety, clinical and cost effectiveness of treatment by homeopaths and nutritional therapists for children with ADHD
- assess the feasibility of the TwiCs design to efficiently test the comparative acceptability, clinical and cost effectiveness of a wide range of treatments for children with ADHD by conducting a small-scale test of the methods and procedures
- assess the feasibility of recruiting to time and target a cohort of children with a diagnosis of ADHD
- assess the suitability, acceptability, and deliverability of the outcome measures
- inform the sample size calculation for a full trial

1.4 The audience for my research

The audience for my research are those who make decisions and recommendations about treatment options and ways to improve outcomes for those with ADHD. This includes carers, local councils, health professionals, ADHD researchers and ADHD research funders. A key audience is the National Institute for Health and Care Excellence (NICE) since families with children with ADHD tend to access health care provided free at the point of delivery by the National Health Service (NHS). NICE assesses which treatments produce sufficient benefit that the NHS should pay for them (https://www.nice.org.uk/about). Whilst guidelines are advisory and do not have legal force, they are very influential (Taylor, 2008).

1.5 Rationale for the thesis

An overview of the rationale for this thesis is provided here, with reference to sections in the thesis where the subject is discussed and referenced in depth.

1.5.1 ADHD

Improvement in the outcomes of those with ADHD is important from the perspective of the child, their family, and society. Children with ADHD are more likely to be in care, to suffer from post-traumatic disorders, have poor social skills and are at higher risk of negative outcomes such as involvement in violent crimes, particularly at a young age (section 2.2). This negative trajectory tends to start at school, where children with ADHD are more likely to be disruptive, excluded, low achievers and/or drop out, all of which are known risk factors for criminality, substance misuse and psychiatric disorders (section 2.2.4).

Teenage years are particularly difficult for those with ADHD. They tend to stop taking their ADHD medications (section 2.3.1). At school they experience increased pressure to study for national exams, but tasks become less suited to them, particularly when distant completion dates are given for homework and longer-term application is required. They experience hormonal changes which exacerbate their emotional dysregulation. As with all teenagers,

they are increasingly influenced by peers and decreasingly influenced by carers, but their ADHD means they are less able to replace the supportive structure carers may have provided with their own structures.

Families with children with ADHD are affected. Siblings experience elevated levels of bullying. Parents are more likely to divorce, have drug and alcohol associations, affective disorders or suffer from stress (section 2.2.2).

Management of these issues strains education, health, criminal justice and social care systems. The highest costs are found in education (section 2.2.6) because in school children require considerable extra input compared to those without ADHD. ADHD is the most common reason for a referral to Child and Adult Mental Health Services (CAHMS) accounting for 35.7 % of presentations (Health Service Executive (HSE), 2012) (Hayden, Flood, & McNicholas, 2016) and the most common reason for a follow up by UK CAMHS (Woodward, Dowdney, & Taylor, 1997). It is the largest risk factor for early criminality, and for disruptive behaviour in prisons (section 2.2.4).

Effective treatments are needed to help children with ADHD, and the earlier the better if the spiral of negative outcomes is to be prevented.

1.5.2 Mainstream Treatment

Diagnosis, treatment and management of ADHD occurs primarily within the NHS, but education, social care and criminal justice systems are also involved in treatment and management.

NICE guidance post ADHD diagnosis (National Institute for Health and Care Excellence (NICE), 2008) is to provide self-instruction manuals based on positive parenting and behavioural techniques, and stress the value of a balanced diet, good nutrition and regular exercise. The first line of treatment for pre-school children and those with moderate impairment is the offer of parent training or education programmes. The guidance states that drug treatment should only be offered to those severely impaired, and as the second line of treatment for those with moderate impairment who have refused or not responded sufficiently to behaviour change programmes. In reality the majority of children are offered drug treatments after participating in behavioural programmes (section 2.3).

Evidence suggests that both pharmaceutical and behavioural treatments are only effective whilst implemented and that compliance is poor, with teenagers particularly prone to discontinuing them (section 2.3). Medication is only licenced from age 6 in the UK, although ADHD symptoms often manifest well before this age (NICE, 2008). Up to 25% of children do not respond to stimulant medication or behavioural interventions, particularly those with

concomitant ADHD and autism spectrum conditions (ASCs); and side effects of medication, such as nervousness, trouble sleeping, loss of appetite, weight loss, dizziness, nausea, vomiting, mood swings, or headache, are common (www.NHS.uk) (section 2.3.1).

There are long waiting lists for some NHS services, and patchy provision throughout the UK. Furthermore, associated co-morbidities are treated separately and drug side effects may also need treatment. For example, stimulant medication increases dopamine levels in the brain which may exacerbate sleep problems (section 2.3.1), leading to prescription of off-label Melatonin.

1.5.3 Non-mainstream treatments.

These are treatments outside the realm of mainstream medicine. They are referred to in a variety of ways. For example as unconventional (Ng & Weisz, 2016), Complementary and Alternative Medicine (CAM) (Hall & Riccio, 2012), and Integrative Medicine (when conventional and complementary approaches are brought together in a co-ordinated way" (https://nccih.nih.gov)).

The most popular interventions across surveys of ADHD are: supplements, dietary changes, acupuncture, homeopathy, massage, craniosacral therapy, music therapy, equine therapy, secretin (a regulatory hormone) and chelation (a detoxification treatment) (section 2.3.4). The interventions are varied: some have been around for a long time (e.g. acupuncture, massage) but we don't know how effective or relevant they are to ADHD; some therapies involve touch (craniosacral therapy); needles (acupuncture), some no touch (music therapy); some involve ingesting something (homeopathy, supplements); some involve modifying what is ingested (Gluten Free, Casein Free diets).

Doctors are found to be uncomfortable recommending treatments about which they are unknowledgeable and untrained, without supportive empirical evidence (Akins, Angkustsiri, & Hansen, 2010), although a recent survey found that they had a high interest in using natural medicines in paediatrics (Huckstadt, 2017). Nevertheless, the use of non-mainstream treatments is increasing despite the concerns of physicians, and in addition to medication (section 2.3.4). Increases are especially seen where medical treatment is associated with adverse effects and for children with chronic conditions, which ADHD is considered to be. It is likely that non-mainstream interventions remain outside the mainstream whilst their evidence base is poorly developed (section 2.3.4).

Whilst the majority of carers of children with ADHD rely on treatments provided free at the point of delivery by the NHS, a number are trying other treatments and paying for them out of their own pocket (section 2.3.4). It is important that these non-mainstream approaches are assessed to see whether they might be supportive in the management of ADHD for sev-

eral reasons. Carers are trying them, and evidence can inform their choices. Doctors need evidence in order to recommend them. And adjunctive novel treatments are required to address gaps in provision and reduce the burden on children, their families, and key social institutions.

The lack of evidence, and its poor quality, are reasons why non-mainstream treatments remain outside the realm of conventional medicine. The following section looks at reasons why evidence is considered poor quality, and introduces key concepts for assessing the quality of evidence.

1.5.4 Assessing and testing treatments

The concept of validity was formulated by Kelly (Remmers, Shock, & Kelly, 1927) who stated that a test is valid if it measures what it claims to measure. Three types of validity are seminal to this thesis: internal, external and ecological validity.

A key consideration for assessors is the internal validity of trials. Internal validity refers to the extent to which the methods used to test an intervention are free of potential for bias. Explanatory trials, which aim to evaluate the efficacy of an intervention (that is whether it demonstrates positive benefits over a placebo or another intervention when tested under ideal conditions), tend to have high internal validity. This is because they have less potential for bias, and greater confidence that the results obtained are down to the measured intervention.

Pragmatic trials aim to test the effectiveness of an intervention, that is whether it works in everyday practice. Such trials tend to have high external validity. External validity refers to the extent to which the methods used to test an intervention are generalizable to real-world settings.

Internal validity is prioritised by assessors and considered a pre-requisite before external validity is considered (Section 3.1.5) (Torgerson & Torgerson, 2008). NICE assessment procedures equate explanatory designs with study excellence. Good internal validity provides increased confidence in the effects measured. Unblinded, pragmatic studies are considered de facto low quality. Because researchers tend to prioritise internal validity when designing trials, tests of real-world effectiveness are few.

This is problematic because it means that interpretation of an intervention's effectiveness is influenced by its ability to be tested using trial designs with high internal validity such as double-blinded randomised placebo-controlled trials (RCTs), considered the gold standard of the evidence base. Interventions tested using pragmatic designs, appropriate for the assessment of behaviour change programmes and most non-mainstream interventions, may

not be recommended by health care decision makers due to their de-facto poorer internal validity.

Ecological validity refers to the core principles and concepts of an intervention. It refers to the extent of concordance between a trial design and the core principles of the intervention tested. The extent to which they are represented in a trial is important to assess the generalisability of results regarding that intervention.

Many non-mainstream treatments are considered complex, holistic, are individually tailored, and/or therapist led. They tend to have interacting components that require viewing and testing as a synergistic network to achieve adequate ecological validity (Medical Research Council (MRC), 2000). This presents a challenge for trial designers in the context of the supremacy of the double-blinded placebo-controlled RCT. Researchers therefore tend to focus on identifying an active ingredient using reductionist strategies (Verhoef, Mulkins, & Boon, 2005). It has been identified that this is mitigating against the development of an appropriate evidence base (Saks & Robinson, 2015) (MRC, 2000), and may be obscuring the fact that patients are helped by such types of interventions.

A further consideration is that holistic or whole system approaches expect non-specific outcomes. Their potential is considered to be to "promote and enhance wellbeing, resilience, and the realisation of an individual's potential capacities for self-care, self-regulation and self-healing" (http://www.nhsggc.org.uk). Such effects may not be captured using treatment-specific outcome measures (for example (Fibert, 2015a)).

Individually tailored treatments may be particularly suitable for those with ADHD due to the condition's heterogeneity and association with co-morbidities. Individually tailored approaches are delivered based on individual characteristics and preferences, and adjusted over time to optimize outcomes. Addressing multiple diagnoses through a single individually tailored therapeutic intervention may offer value for money as well as improved outcomes.

However, running such trials is expensive, and funding difficult to procure, so often trials are small and underpowered. It can be difficult to standardise delivery when testing individualised interventions, which are therapist led. Such trials are vulnerable to therapist effects and reduced model validity. Model validity is the extent of concordance between the trial study design and ideal practice (Mathie, van Wassenhoven, Jacobs, & Oberbaum, 2015). Furthermore, since interaction between therapist and patient is an essential component of treatment, patients cannot be blinded to the intervention they receive.

This research aims to facilitate a rigorous research facility to test all treatments being used by families, both main and non-mainstream, to provide useful information for key stakeholders.

1.5.5 Rationale for the trial design

Traditional double-blinded, placebo-controlled designs are very good at testing the specific effects of interventions, particularly drugs. Isolating their effects can provide knowledge for further development of existing treatments, development of novel interventions, and confidence that the effects measured are due to the variable tested. They are at reduced risk of bias, meaning that there is less chance that a known or unknown variable(s) may be responsible for the observed effect other than the intervention.

In achieving methodological purity, direct relevance to clinical practice may be sacrificed. And such testing is unsuitable for exploring either the efficacy or effectiveness of complex, holistic, and/or individually tailored interventions. When such tests are applied, they do not test the efficacy of that intervention – that is its performance in an ideal situation. Rather, circumstances in such trials are the opposite of ideal because isolation of any of their intertwined, inextricably linked variables severely compromises ecological validity, as does standardisation of delivery in therapist-led interventions.

To provide suitable information to enable the comparative evaluation of the effectiveness of treatments for ADHD to improve outcomes, a pragmatic (not explanatory) trial of effectiveness (not efficacy) measuring real-world outcomes of interest (not surrogate markers, or just ADHD symptoms) is appropriate. Traditional double-blinded, placebo-controlled designs are unsuitable to answer questions about real-world effectiveness and cost effectiveness, or to compare all types of intervention.

Key requirements of a potential pragmatic trial design are: to test treatments as delivered in the real-world in heterogeneous patient samples; to measure patient and stakeholder centred outcomes; to use real-world comparators; to be suitable to test multiple, diverse interventions comparatively; and to be acceptable to stakeholders (chapter 3). This means external and ecological validity should be high, as treatment resembles that experienced in routine health care. The challenge with pragmatic trials is to provide a good balance of internal, external and ecological validity. Full generalizability can result in unreliable results, whilst the attempt to achieve methodological purity can result in clinically meaningless results, so achieving a creative tension is crucial.

The TwiCs approach

Key features of the TwiCs approach are the recruitment of a large observational cohort of people with the condition; regular measurement of outcomes for the whole cohort; and the capacity for multiple randomised controlled trials over time. For each RCT, eligible participants are identified from the cohort and some are randomly selected to be offered the trial intervention. The outcomes of the randomly selected patients are compared with the

outcomes of eligible participants not selected (that is, receiving usual care). The process of obtaining patient information and consent aims to replicate that in real-world routine health care (Relton, O'Cathain, Nicholl, & Torgerson, 2010).

The approach enables reliable comparisons compared with trials using current RCT designs because all treatments have the same 'treatment as usual' comparator and measure the same outcomes. This is particularly pertinent in trials of ADHD where the two main treatment categories (behavioural and pharmaceutical) require different trial designs, which are difficult to compare due to differing validity and consequent expectation of different effect sizes, and have different comparators.

The design can provide useful, generalisable information to stakeholders because: it measures relevant real-world outcomes; the experience of participating in a trial closely resembles routine care in that information about, and consent to try, potential treatments is provided as and when they are offered; and data on treatment refusers provides information on the acceptability of the treatment. Lower costs are incurred compared with standard designs, since once the cohort is established, it potentially allows rapid and cheap recruitment of patients for an RCT.

The design may facilitate easier recruitment since there is no commitment or uncertainty about joining the cohort. Not only may lack of uncertainty improve recruitment, but participants are not told about treatments that they might not then receive, nor that their treatment will be allocated by chance. Recruitment and follow-up are more characteristic of longitudinal observational studies.

However, the design is still vulnerable to risk of bias, since many other potential variables are not controlled for. Since the offer of treatment is adjunctive, participants may be undertaking other therapies which may influence results. Nor will it be possible to know which aspect of treatment was most influential, for example, whether therapist effects drove outcomes.

1.6 Thesis Design

So far I have summarised the rationale for the doctoral work undertaken. I have described my background and explained why I have chosen to undertake this research. I have summarised some of the problems affecting those with ADHD and those taking care of them, and the areas of unmet need. I have briefly described the mainstream treatments recommended by NICE and provided by the NHS, and the non-mainstream treatments carers are also using for their children with ADHD. I have explained why there is a need to rethink the way trials are conducted in order to obtain useful, comparative information about interventions to

improve outcomes. The TwiCs design is then described as a methodology which can potentially provide such information.

In the next chapter I describe ADHD and its impact in more depth: its impact on individuals and on family life, and the financial and social challenges the condition presents to public service providers. I look at current service provision in the UK and at treatments recommended by NICE. I interrogate the evidence for the efficacy of pharmaceutical medication and behaviour change programmes in short-term studies and their long-term effectiveness.

I explore the problems associated with current provision: evidence suggesting that children do not take pharmaceutical medication for extended periods; that medication has common side effects; that short-term evidence of efficacy may not translate into long-term effectiveness; that provision of behavioural interventions is patchy across the country, costly, associated with attrition, and may only be effective whilst implemented.

I argue that the condition is associated with long-term negative outcomes, which are not being impacted despite increases in provision of pharmaceutical medication. I suggest that novel interventions with the potential to improve areas of unmet need are needed.

Non-mainstream treatments being used by carers are suggested as a starting point for such a search. I review surveys of the interventions being used and select the therapeutic systems of Homeopathy and Nutrition as two treatment modalities being used with some preliminary evidence supporting them.

In chapter 3 I explore trial design issues in depth, to elucidate the necessary components of a trial design to achieve my stated aim of testing whether interventions might improve outcomes. I look in more depth at the strengths and weaknesses of pragmatic and explanatory designs, focussing particularly on internal, external and ecological validity and the tensions across these. I explore how best to maximise and balance these tensions. Key requirements identified are that the effectiveness of real-world treatment is tested; that the sample is representative; that potential biases are controlled for; that effectiveness in areas of unmet need is measured; that outcomes are measured over the long-term; and that there is adequate control, but not by placebo.

A pragmatic trial design is identified as most suitable because it uses real-world treatment protocols; patient and stakeholder centred outcomes; heterogeneous patient samples; and real-world comparators. The implications of these for a trial of ADHD are discussed, and the TwiCs approach identified as being most appropriate to test whether multiple interventions might improve outcomes for children with ADHD. The advantages and disadvantages of the design, potential outcome measures, and recruitment strategies are explored.

Chapter 4 is a literature review of one of the interventions trialled - the therapeutic modality of homeopathy, considered a holistic, complex, non-specific intervention. Issues surrounding the evidence base are discussed, particularly the poor ecological validity of trials to date. To know whether homeopathic treatment might improve outcomes, it is identified that the totality of the therapeutic system as experienced in real-life clinical practice needs to be tested. This intervention is termed 'treatment by a homeopath' and consists of a series of potentially therapeutic consultations and provision of individually tailored homeopathic remedies.

Chapter 5 is a literature review of the other intervention trialled - Nutritional Therapy. The theoretical basis for a nutritional approach is explored and the evidence base for the different aspects of nutrition which have been tested is reviewed. A lack of comparative research studies testing the totality of the intervention, and the limitations of existing explanatory studies to provide suitable information for stakeholders about the effectiveness of a nutritional approach is identified.

The intervention is termed 'treatment by a nutritional therapist' and considered to consist of a series of potentially therapeutic consultations, advice about dietary exclusion and inclusion, menu and lifestyle suggestions, and advice about and provision of individually tailored supplements.

A fundamental tension between internal and external validity is found across the evidence base for both treatments, whereby studies representing optimal clinical treatment are considered at risk of bias and studies with reduced risk of bias do not represent clinical treatment and are therefore inadequate to answer pragmatic stakeholder questions.

Chapter 6 describes the methods used to address the research question of this thesis: "Is the TwiCs design feasible to generate evidence about the acceptability, clinical and cost effectiveness of interventions for ADHD?" A small-scale test of the methods and procedures to assess the feasibility of the design and interventions according to a priori specified parameters is described.

The chapter describes the recruitment procedures to the observational cohort, named the STAR (Sheffield Treatments for ADHD Research) cohort. The functional procedures for the three-armed pilot trial embedded in the cohort are then described, whereby (a) treatment by homeopaths and (b) treatment by nutritional therapists is compared to (c) treatment as usual. Study management procedures such as ethical consents, research governance, steering and management committee structures are outlined, including how potential risks are identified and managed.

Feasibility criteria and parameters are defined: the feasibility of recruiting a cohort of children with a diagnosis of ADHD to time and target; recruiting therapists; the feasibility and acceptability of the study design; the feasibility, deliverability, safety and acceptability of the interventions; and the suitability, acceptability and deliverability of the outcome measures.

Chapter 7 describes the results of recruitment to the cohort, and the pilot trial. The baseline characteristics of cohort participants, those randomised to treatments, and those having treatments, are compared for any systematic differences in population characteristics.

Statistical analysis compares the interventions with usual care according to Intention to Treat (ITT) analysis using two methods: standardised mean differences to assess the clinical impact and calculate an effect size to enable sample size calculation; and multivariate regression analysis, controlling for the effects of gender, age and ADHD severity, to assess statistical impact and calculate the unstandardised coefficients which will enable the cost effectiveness analysis.

The primary outcome is Conners Global Index (CGI) and its two sub-scores assessing restlessness/impulsivity and emotional lability. Health related quality of life is also measured, using the Child Health Utility (CHU 9D) with preference weights added.

Chapter 8 explores the feasibility of the design and interventions according to the 13 a priori specified criteria. The characteristics of the STAR cohort are described to assess the representativeness of the cohort. Rates of recruitment to the cohort and the RCT are described to identify whether recruitment was achieved within the specified time frame. Rates of uptake and attrition from treatments, and the safety of the interventions assesses their acceptability. The acceptability and suitability of outcome measurements looks at levels of missing items. Whether suitable therapists could be recruited and deliver their interventions is described, and therapists' experiences summarised.

In chapter 9, the research aims and context are reviewed and discussed. The feasibility of the TwiCs design is discussed in terms of its ability to recruit a representative sample of children with ADHD and measure their outcomes of interest, and to serve as a recruitment facility for multiple trials of interventions for ADHD. Whether the design is feasible to generate evidence about the acceptability, clinical and cost effectiveness of interventions for ADHD is discussed by exploring the strengths and limitations of the pilot RCT. The strengths and weaknesses of the TwiCs design to contribute to areas of unmet need is discussed, and suggestions to improve implementation of the design are made.

Chapter 10 summarises the key findings and their potential contribution. The results in the context of the current political, economic and social climate are discussed, and some proposals for next steps outlined. Recommendations to improve recruitment, adherence, out-

come measurement and outcome collection are made. The implications of the results regarding progression to a full trial, and the future contribution of the STAR cohort are discussed. This chapter also includes a summary of my contribution to the conducted research, and my learning from the research endeavour.

Chapter 2 ADHD

This chapter describes the diagnosis of ADHD, and the short and long-term impact of a diagnosis on the child, their family, and the education, social services and criminal justice systems. It outlines the nature of the problems that need to be addressed if outcomes for children with ADHD are to be improved. The second half of the chapter explores the evidence base for both main and non-mainstream interventions being used as treatments for children with ADHD.

To do this I first read the NICE clinical guideline to diagnosis and management, originally published in 2008, and updated in 2016. This guideline provided a framework from which to explore issues highlighted by NICE in more depth, and enabled the identification of key researchers and research hubs. I then explored their work, and further augmented this with information gained from systematic reviews on specific topics of interest found through Web of Science, Google Scholar, and Cochrane collaboration searches for ADHD. I also attended two International ADHD conferences and two NICE workshops.

When exploring the impact of ADHD on families and children is explored across the health system, education services, criminal justice system and social care system, I looked at what is offered by services, and what aspects of ADHD are and aren't being helped by current provision within these systems. Where possible, UK statistics and evidence are used. Evidence from other countries is referred to where no UK evidence is found. The most recent research and statistics are referenced where possible, however, much of the work defining and describing ADHD occurred in the 1990s.

2.1 Description of ADHD

2.1.1 Diagnosing ADHD

The Diagnostic and Statistical Manual of Mental Disorders (DSM) lays out the criteria used by health professionals making a diagnosis of ADHD (American Psychiatric Association, 2013). Diagnosis considers the behavioural symptoms of inattention, hyperactivity, and impulsivity from the perspective of the observing clinician, the child's home and school. Children need to have been displaying symptoms for at least six months starting before the age of 12 in at least two settings.

Those with a diagnosis of ADHD have difficulties with problem solving, planning, flexibility, sustained attention, response inhibition, working memory, motivational delay and mood regulation. They may have feelings of irritability, frequent outbursts, shifts from normal

mood to depression or excitement, a diminished ability to handle typical life stresses. These result in frequent feelings of being hassled and overwhelmed.

A diagnosis may be classified into different subtypes: 'predominantly inattentive'; predominantly hyperactive-impulsive; or 'combined' types. These classifications are debated, as is whether ADHD is indeed a single disorder For example, some suggest that combined types and inattentive types are distinct and unrelated (Barkley; 1997; Milich, 2001). Others debate whether the same diagnosis of ADHD should be given to both traumatised and untraumatised children, where high levels of co-occurrence are found (Arshad, 2008; Wozniak, 1999).

Whilst it is classified as a separate disorder, possibly because clinicians make categorical decisions, it may be more accurate to consider it an umbrella term or an extreme of normal variation. Furthermore, a diagnosis is often an indication that there are other problems (Sonuga-Barke, in NICE, 2008).

Co-diagnoses

Criteria have changed over time. In 2013 DSM-5 allowed co-diagnoses of ADHD and autism, and since then many autistic children have received a diagnosis of ADHD. Initially emotional issues were considered core features in diagnosis (Clements, 1966; Wender, Reimherr, & Wood, 1981), however, since DSM-3 emotional lability has been considered an associated feature rather than a diagnostic criterion (Shaw, Stringaris, Nigg, & Leibenluft, 2014). Co-morbid emotional issues receive separate diagnoses such as Oppositional Defiant Disorder, Conduct Disorder, Depression, Anxiety, and Attachment Disorder.

Co-diagnoses are common. They were found in 40% of participants in the Multimodal Treatment of ADHD (MTA) study (MTA Cooperative Group, 1999). Psychiatric co-diagnoses were found in 65% of children in a meta-analysis of amphetamine-based treatment for ADHD (Punja, et al., 2016). A meta-analysis of methylphenidate treatment found that oppositional defiant disorder was the most commonly reported comorbidity (61 trials; range 1.4% to 84%; mean 42%), followed by conduct disorder (49 trials; range 0% to 100%; mean 24%) (Storebo, et al., 2015).

Other co-diagnoses include: learning disorders (25% co-morbidity); neurological disorders such as tics and Tourette's Syndrome (60%) (Gillberg, et al., 2004); anxiety disorder (33%), and depression (33%) (Mayes, et al., 2009); autism (50-75%) (Goldstein & Schwebach, 2004; Aman, Farmer, Hollway, & Arnold, 2008; Gadow, De Vincent, & Pomeroy, 2006).

The prevalence of obesity is 40% higher in children and 70% higher in adults with ADHD compared with individuals without ADHD (Cortese, et al., 2016).

Autism Spectrum Conditions (ASCs)

Autism is a common co-diagnosis (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008), and ADHD medications are widely prescribed. However, children with autism and ADHD may be more prone to the side effects of medication and experience less benefits than those with ADHD alone (Handen, 2000).

Emotional dysregulation

It has long been recognized that emotional dysregulation is common in ADHD. Emotional difficulties are described as falling into three categories: emotional dysregulation inherent in the disorder; comorbidity with other psychiatric disorders; and secondary emotional consequences from impairments arising from the effect of ADHD and the comorbid disorders on the social environment (Wehmeier, Schacht, & Barkley, 2010).

Emotional dysregulation is defined as inappropriate excessive emotional expression, with rapid, poorly controlled shifts in emotion (lability), and anomalous allocation of attention to emotional stimuli (Shaw, Stringaris, Nigg, & Leibenluft, 2014). Responses may be internalised (withdrawn, moody, or sad) or externalised (volatile, aggressive, argumentative, and physical) (van Stralen, 2016). It is estimated to occur in 25%-45% of children and 30%-70% of adults with ADHD (Ana, Soriano, Fernandez, & Melia, 2008).

2.1.2 Aetiological factors

The aetiology of ADHD is considered to involve the interplay of multiple genetic, biological, psychosocial and environmental factors. These risk factors increase vulnerability additively and interactively, and once cumulative vulnerability exceeds a threshold, ADHD symptoms manifest. Its heterogeneity is considered to result from different combinations of risk factors acting together, with no one causal factor considered sufficient to initiate the disorder (Biederman & Faraone, 2005).

Genetic heritability is estimated at 71-75% (Faraone, Perlis, & Doyle, 2005; Nikolas & Burt, 2010). Associated identified environmental influences are diverse, with increased incidence associated with exposures during pregnancy, birth, and post birth. Increased incidence in children has been found during pregnancy if their mothers: smoked (Linnet, Dalsgaard, & Obel, 2003; Silva, Colvin, & Hagemann, 2014); used alcohol (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002); drugs (Ornoy, Segal, & Bar-Hamburger, 2001); paracetamol (Liew, Ritz, & Rebordosa, 2014); cell phones (Birks, et al., 2017); and/or were exposed to lead or pesticides (Rauh & Margolis, 2016).

Adverse experiences during childbirth implicated include: maternal urinary tract infection, birth induction, experience of threatened pre-term labour (Silva, Colvin, & Hagemann, 2014); very low birth weight (Botting, Powls, Cooke, & al., 1997); foetal hypoxia, and brain injury (Toren, Eldar, Sela, & al., 1996; Ana, Soriano, Fernandez, & Melia, 2008).

Correlated post birth psychological influences include: severe early psychosocial adversity (McCann & Roy-Byrne, 2000); disrupted and discordant relationships (Biederman, Newcomb, & Sprich, 1991); severe institutional deprivation (Kennedy, et al., 2016), low paternal education, low income and maternal depression (Sagiv, Epstein, Bellinger, & al., 2013). However, whilst adverse familial environments and parenting practices are observed in families of children with ADHD (Johnston & Mash, 2001), the extent to which they are casual factors remains unclear, and longitudinal evidence mixed (Tarver, Daley, & Sayal, 2014).

2.1.3 Pathology of ADHD

ADHD is a neurobiological condition linked to an imbalance in neurotransmitters (often epinephrine, norepinephrine, serotonin or dopamine) within the prefrontal cortex of the brain (Hoogman, 2017). These neurotransmitters are responsible for activating the areas of the brain needed for focus and concentration. A precise mechanism remains unclear, but neuroimaging studies show structural alterations in several brain regions (Hoogman, 2017) with exploratory lifespan modelling suggesting delay in maturation. Regions are found to be underactive and with weakened connections to other parts of the brain (Arnsten, 2009).

Suggestions of possible physiological causes of low levels of neurotransmitters include: dysfunction in the manufacture of necessary compounds; their poor uptake into the brain; or increased transport out of the brain. Studies have found abnormalities and disturbances of glutamate/glutamine and creatine in the brain (Perlov, Philipsen, Hesslinger, & et, 2007; Carrey, MacMaster, Gaudet, & Schmidt, 2007). Essential fatty acids and phospholipids are both essential for normal neuronal structure and function (the myelin sheath insulating brain neurons is 75% phospholipids). This underlying abnormality of fatty acid synthesis may be responsible for at least some features of ADHD (Richardson & Puri, 2000). This theory is explored in greater depth in chapter 5 (Nutrition).

Despite emerging neurocognitive theories concerning pathology, there are currently no neurological markers for ADHD, nor likely to be. The disorder is defined by behaviour and diagnosis does not imply neurological disease.

2.1.4 Prevalence of ADHD

Global prevalence of ADHD is estimated at 5.3% (Polanczyk, de Lima, Horta, & al., 2007), 5.9% (Willcutt, 2012) to 7.2% (Thomas, Sanders, Doust, Beller, & Glasziou, 2015). UK prevalence was estimated to be 3.6% for boys and 0.9% for girls (Ford, Goodman, & Meltzer, 2003). Recent prevalence estimates from the Millennium Cohort Study using 2008/2009 data found 1.4 % had ADHD, 1.7 % had an ASC, and 0.3 % had both (Russell, Rodgers, Ukoumunne, & Ford, 2014).

Increased prevalence is noted with each edition of the DSM (Polanczyk, de Lima, Horta, & al., 2007). Increased medication usage is also noted: methylphenidate prescriptions increased from 420,421 in 2007, to 793,749 in 2014 (NICE guideline update document, 2016).

2.2 The impact of ADHD

ADHD impacts significantly over the life span, on the separate disciplines of health care, education, criminality and social work. The most destructive consequences are arguably experienced within the home by individuals and families. Those diagnosed in childhood continue to show significantly worse educational, occupational, economic, and social outcomes three decades after initial diagnosis compared with age-matched controls (Klein, et al., 2012). It accounts for a sizeable amount of resource use and presents a major challenge to services (NICE, 2008).

The association of ADHD with a variety of negative outcomes can be summarised as: academic failure; interpersonal relationship difficulties; reduction in quality of life; increased susceptibility to injury; substance abuse; involvement with the criminal justice system; and greater socioeconomic disadvantage (Russell, Ford, Rosenberg, & Kelly, 2014).

2.2.1 Impact on the child with ADHD

Children with ADHD struggle to fit in at home, where increased parent-teen conflict is reported by both parents and teenagers (Edwards, Barkley, Laneri, Fletcher, & Metevia, 2001) and at school, where they typically experience academic failure, rejection by peers and low self-esteem (Harpin, 2005). They often have few friends (Gresham, MacMillan, Bocian, Ward, & Forness, 1998); are twice as likely to have ‘‘a severe lack of friendship’ (Meltzer, Gatward, Goodman, & Ford, 2000); to be rejected by peers (Hoza, et al., 2005); to be perceived by teachers and peers as being less socially competent (DuPaul & Weylandt, 2006); and to experience more conflicts with peers and teachers (Faraone, Biederman, & Monuteaux, 2000). Many studies have found them to have poor social skills, e.g. (Bagwell, Molina, Pelham, & Hoza, 2001).

ADHD children are more likely to hurt themselves as pedestrians or cyclists, and sustain injuries to multiple body regions (DiScala, Lescohier, Barthel, & Li, 1998). The more than double mortality found in those with ADHD compared to those without ADHD is driven by deaths from unnatural causes, especially accidents (Dalsgaard, et al., 2015). They have less sleep: 25-50% have sleep problems (Owens, 2008), with more severe and prevalent sleep problems occurring in stimulant treated ADHD children than untreated children (Mohammadi, et al., 2012). They are less happy with their family and their lives overall than children without ADHD, with health-related quality of life about 6% lower (Peasgood, et al., 2016).

Those with ADHD and emotional problems are significantly more impaired in peer relationships, family life, occupational attainment, and academic performance than those with ADHD alone (Barkley, Murphy, & Fischer, 2010; van Stralen, 2016). For example, emotional problems have more impact than hyperactivity and inattention on well-being and self-esteem (Riley, et al., 2006). They are better indicators of impairments in daily life than the level of ADHD (Melia, et al., 2006).

Emotional dysregulation presages poor clinical outcome (Ana, Soriano, Fernandez, & Melia, 2008; Green, Gilchrist, Burton, & Cox, 2000; Smalley, McGough, Moilanen, & al., 2007), and is a key factor in predicting later adverse life events (Barkley & Fischer, 2010). Persistence of ADHD is predicted by co-morbid psychiatric disorders (Ana, Soriano, Fernandez, & Melia, 2008; Barkley R. A., Fischer, Smallish, & Fletcher, 2004). Smalley et al. found it to be associated with anxiety (odds ratio 2.4), mood (odds ratio 2.9) and disruptive behavioural disorders (odds ratio 17.3) (Smalley, McGough, Moilanen, & al., 2007).

2.2.2 Impact on the home of the child with ADHD

Having a child with ADHD is a risk factor for a variety of problems to be experienced by other members of the family. Studies have found it to be a risk factor for depression and substance abuse in parents (Cunningham & Boyle, 2002), marital conflict (Stormont-Spurgin & Zentall, 1995), and divorce (Schermerhorn, et al., 2012). It is hard to separate cause and effect. Given the heritability of ADHD it is likely that the relationship between parenting and child ADHD is bi-directional (Tarver, Daley, & Sayal, 2014).

Siblings report feeling victimised by aggressive acts of their sibling with ADHD (Kendall, 1999) and experience lower happiness with life overall and with their family, and elevated bullying (Peasgood, et al., 2016). Siblings have been found to be at increased risk of conduct and emotional disorders (Szatmari, Offord, & Boyle, 1989).

2.2.3 Impact of having ADHD on education

School is frequently the first place where concern is raised leading to an ADHD diagnosis, because typical ADHD symptoms are a major disruption in the classroom and playground. Children may exhibit challenging classroom behaviour, significant time off-task, frequent rule violations, and fail to comply with teacher instructions (Atkins, Pelham, & Licht, 1989).

A diagnosis of ADHD is associated with poorer grades and lower scores on standardized tests of academic ability compared to those without a diagnosis (Barry, Lyman, & Klinger, 2002; Loe & Feldman, 2007). Up to 30% of children in the US repeat a grade in school (Barron, Evans, Baranik, Serpell, & Buvinger, 2006); and 10-35 % drop out (Barkley, 2006). Children with Special Educational Needs (SEN) (including ADHD) are over eight times more likely to be permanently excluded than pupils with no SEN (Department for Education and Skills, 2005); and a survey of 526 UK ADHD families (www.addiss.co.uk) found 39% had had fixed term exclusions, and 11% were permanently excluded. A study by the Office for National Statistics found having ADHD increased the odds of a child having been excluded by 11 times (Meltzer, Gatward, Corbin, Goodman, & Ford, 2003).

Children with ADHD have been found to be more impaired in behaviour, academic skills and social skills (Greenhill, Posner, Vaughan, & & Kratochvil, 2008). They often have associated learning difficulties such as increased deficits in early language development, literacy, and numeracy skills (DuPaul, McGoey, Eckert, & Van-Brakle, 2001).

Classroom based interventions can have a positive impact on behaviour although not on educational outcomes (Purdie, Hattie, & Carroll, 2002). Teachers are not systematically trained to use specific strategies (NICE, 2008). Whilst training may not improve outcomes (Sayal, et al., 2010), provision of evidence based information about how to teach those with ADHD type behaviours may (Tymms & Merrell, 2006). Children with more severe ADHD may be entitled to a statement of special educational needs and either a support worker within mainstream education, or a place at a special school. Both incur significantly higher costs compared with regular education.

Conflict between family and school (Mautone, Lefler, & Power, 2011) and teacher and pupil (Greene, Beszterczey, Katzenstein, Park, & Goring, 2002) are common. This puts additional strain on education systems: other children in the classroom are negatively impacted by the behaviour of their ADHD peers; teachers spend a significant amount of time managing and providing support to children with ADHD; children may experience reduced teaching quality when teachers focus on management of disruptive pupils; and teachers find dealing with ADHD behaviours stressful (Merrell & Tymms, 2007).

Children with ADHD have difficulty engaging in typical school activities: making and keeping friends, developing meaningful relationships, interacting appropriately in games, and tend to withdraw from social activities. They are more likely to be nominated by their peers as someone they would least like to be friends with (Hinshaw, 1995; Hoza, et al., 2005).

2.2.4 Relationship with criminality

A relationship is consistently found between ADHD and criminality when studying incarcerated populations (Young, et al., 2011), ADHD populations (Mannuzza, Klein, & Moulton, 2008) and taking an epidemiological perspective (Gudjonsson, Wells, & Young, 2010). Epidemiological studies suggest that ADHD is one of the six key childhood factors predicting offending and antisocial behaviour (Farrington, Loeber, & Ttofi, 2012). In ADHD populations, children are at elevated risk of offending (Barkley, Fischer, Smallish, & Fletcher, 2004).

In incarcerated populations in the UK, there is an ADHD rate of 43% in 14-year-old youths (Young, Wells, & Gudjonsson, 2010). It was found to be the strongest predictor of violent offending, (above substance abuse), with a significantly larger number of offences than other prisoners (Young, et al., 2011) and a significantly younger onset of offending (16 v 19.5 years). Meta-analysis finds that 30.1% of youth and 26.2% of adult prison populations have a diagnosis of ADHD (Young, Moss, Sedgwick, Fridman, & Hodgkins, 2015).

Relationship of ADHD with other risk factors

Whilst it is undisputed is that ADHD is an important risk factor for the development of antisocial behaviour, debate continues regarding its relationship with other risk factors. For example, whether ADHD itself disposes children to antisocial behaviour, or is due to co-occurring Conduct Disorder (CD) or Oppositional Defiant Disorder (ODD) (Polier, Vloet, & Herpertz-Dahlmann, 2012). Heroin and other substances are major risk factors for criminality (Young, et al., 2011). There is a three- to fourfold increase in the risk of substance misuse in children with ADHD, especially with co-occurring CD, and the onset of ADHD is found to precede the onset of substance use (Wilens T. , 2004). In her most recent criminality research, Young (2016) found that despite controlling for emotional disorders, emotional problems were still the most predictive ADHD aspect regarding offending.

Psychiatric problems are over-represented in prisoners (Fazel & Seewald, 2012) with the risk of developing co-morbid psychiatric disorders greater among offenders with ADHD (Young, Sedgwick, & Fridman, 2015). Their meta-analysis found high incidence in incarcerated adult and youth prisoners (see Table 1).

Table 1 - Co-occurring psychiatric disorders in prisoners with ADHD.

	Conduct disorder	Substance use disorder	Mood disorder	Depression	Anxiety disorder	Personality disorder
Adults	29%	74%	66%	55%	68%	60%
Youth	61%	70%	25%	13%	21%	

Information extracted from (Young, Sedgwick, & Fridman, Co-morbid psychiatric disorders among incarcerated ADHD populations: a meta-analysis, 2015).

The pathway to criminality

A diagnosis of ADHD is one of the risk factors associated with criminality along with low socio-economic status, parent conviction, child and mother low IQ, maltreatment, and temperament (UK government Youth Crime Action Plan, 2008), who found that the earlier offending begins, the greater the odds of reoffending. Researchers agree that ADHD is a precursor to the development of other risk factors with a developmental cascade starting with a childhood diagnosis of ADHD, followed by school exclusion, adolescent antisocial disorder, substance abuse and on to criminality (Mannuzza, Klein, & Moulton, 2008; O'Regan, 2009).

2.2.5 Relationship with social services

Children with ADHD can come to the attention of social services for a variety of reasons. There is a high likelihood that their parents will have ADHD, and poor parenting is associated with parents with ADHD (Deault, 2010). Parents are more likely to be unemployed (NICE, 2008); involved in substance abuse (Parker, 2005); and/or suffer from psychiatric disorders such as schizophrenia, substance abuse, depression and anti-social personality disorder (Pfiffner, McBurnett, Rathouz, & Judice, 2005).

Since ADHD children are more likely to be excluded from school, social services become involved. Since alcoholism and drug taking in pregnancy are risk indicators for the development of ADHD, there will be a disproportionally high number of children with ADHD presenting for fostering and adoption when their addicted parents are unable to care for them. Children in foster care were found to be 3 times more likely to be prescribed methylphenidate than children in the community (Zarin, Suarez, Pincus, Kupersanin, & Zito, 1998).

2.2.6 The economic cost of ADHD

An ADHD diagnosis is accompanied by significant cost implications. These have been explored in Europe and the US. Studies in the US found families with ADHD children incurred over twice the per capita total costs compared to matched comparison families: $1465 v

$690 (Guevara, Lozano, Wickizer, Mell, & Gephart, 2001); $2,461 v $1,220 (Swensen, et al., 2003) and $4,306 v $1,944 (Leibson, Katusic, Barbaresi, Ransom, & O'Brien, 2001). Costs included medication expenditure, physician visits and behavioural interventions. The estimated annual total cost of ADHD in the U.S. is more than 50 billion dollars. This is similar to the societal cost of major depression and stroke (Pelham, Foster, & Robb, 2007).

Whilst studies have identified some of the economic implications of the direct, associated and societal costs of ADHD, there are other likely costs which have not yet been assessed such as poor driving, high rates of traffic accidents, increased smoking and drug abuse, increased presence in foster care, foetal alcohol and narcotic syndrome, and decreased life expectancy. Research is also needed to quantify indirect costs to others, such as being the victims of crime, drug incidents or traffic accidents; the impact on non-ADHD children of being in a class with ADHD children; and the health, wellbeing and job persistence of teachers of children with ADHD.

Le (2014) most recently evaluated the economic consequences of ADHD in Europe (Table 2). He found thirteen studies looking at health care costs (n=7); cost to family members (n=1); education costs (n=2); social service costs (n=2); and family productivity losses (n=2).

Table 2. Review of the cost of ADHD in Europe.

	Cost (millions of euros)	Percentage of total cost
Annual national cost	1,041-1,529	71 ADHD patient. 29 family members
Child health care costs	84 -377	8-25
Family member's health care costs	161	11–15
Productivity cost to family members	143-339	14-22
Education	648	42–62
Social service costs	4.3	0.3–0.4

Information extracted from Le (2014)

Doshi (2012) most recently evaluated the economic consequences of ADHD in the USA (Table 3). He found 19 studies looking at costs incurred by children with ADHD or their family (n=11); health care costs (n=13); income and productivity costs (n=9); education cost (n=3); and justice system costs (n=2).

Table 3. Review of the cost of ADHD in the USA

	Cost (billions of dollars)
Annual national cost	143-166
Children	38-72
Children health care	21-44
Children education	15-25
Adults	105-194
Adult productivity and income loss	87-138
Family members	33-43

Information extracted from Doshi, (2012)

The majority of cost lies outside health care. In Europe, education is the costliest category, as are family member ADHD-related health care costs and productivity losses, whilst health care costs of the child, although most investigated, are just 8–25 %, and social service costs 0.3–0.4 %. (Table 2). The fact that most of the ADHD-related costs are outside health care and not restricted to the affected child has important policy-making implications. It is likely that the societal cost is far higher, but is as yet uncounted in Europe (Le, et al., 2014). Identified areas of impact and associated costs are summarised below.

The workplace

Workforce productivity costs in adults with ADHD in the US (Doshi, et al., 2012) were mostly attributable to income losses due to lack of full time employment and/or lower wages. ADHD in adulthood was associated with work-related problems such as poor job performance, lower occupational status, less job stability, and increased absence days.

A European study projecting occupational consequences of children with ADHD when they become adults suggests that those diagnosed in their childhood lose an average €4,486 per year income due to lower wages (Knapp, King, Healey, & Thomas, 2011).

School/Education costs

School exclusion has significant financial consequences: Welsh Assembly Government (wales.gov.uk/statistics-and-research/exclusions-schools), estimated the cost of permanent exclusion at £300,000 per student, attributed to social care, probation, providing alternative education, and loss of future employment prospects, as well as costs to the community. Governmental statistics from 1996 to 1997 found that the cost of excluding students from

schools in England was £81 million compared with £34 million if they had continued with full-time education (New Policy Institute (NPI), 1998).

In one longitudinal study in London, by age 28, children with childhood conduct problems had cost society 3.5 to 10 times more than a comparison group, mainly for costs associated with crime and education (Scott, Knapp, Henderson, & Maughan, 2001).

Costs to families

Children's ADHD is linked with as yet uncounted strains on the carer-child relationship: less marital satisfaction, more marital conflict, high parental stress, depression, and reduced health-related quality of life for family members (Mugno, Ruta, D'Arrigo, & Mazzone, 2007) (Peasgood, et al., 2016). Family members of children with ADHD have 1.6 times as many medical claims as matched controls (Swensen, et al., 2003).

Carers may need to miss work to meet with teachers or take their children to appointments. A study of parent perceptions found that the strongest predictor of whether they considered ADHD a serious problem was the impact of the child's behaviour on their employment patterns or chances of a career. Parents who perceived their child's ADHD to be a serious problem were 17.6 times more likely to say that their child's ADHD had a financial impact related to their work than carers who did not think ADHD was a serious problem (Sayal, Taylor, & Beecham, 2003).

Criminality

One study estimated the economic impact of criminality associated with ADHD to be $12,868 versus $498 (Swensen, et al., 2003). In the UK, costs to the criminal justice system were £20,000 compared to £200 for those without the disorder (http://www.adhdandjustice.co.uk/). The average annual cost of providing a prison place is £36, 000, rising to £57-£100,000 for young offenders (Prison Reform Trust, 2013). It costs £4,000 per child per annum to teach a child in a mainstream school, but £15,000 per child per annum in a Pupil Referral Unit.

2.2.7 Summary of the impact of ADHD

This section has described in detail the profound impact that having a diagnosis of ADHD has upon the health, wellbeing, employment, finances and prospects of diagnosed children and their families. Furthermore, significant costs are incurred to the different services managing them. It is likely that costs are even higher than estimated since most health economic studies look at health related costs, and the majority of the impact is felt outside health care.

The prospects of those diagnosed in childhood continue to be significantly worse than those of undiagnosed children into adulthood. A pathway towards criminality is likely to start with a diagnosis of ADHD and accompanying emotional dysregulation.

In the next section I will describe the evidence base for the management and treatment strategies currently used to try and help those with ADHD, focussing particularly on their ability to address the negative long-term outcomes associated with the condition described in this section.

2.3 Interventions for managing ADHD

There is currently considered to be no cure for ADHD. Pharmaceutical and non-pharmaceutical treatment options are offered for symptom management and to improve function. Pharmaceutical treatments include both stimulant and non-stimulant options, while recommended non-pharmaceutical treatments include a variety of behaviour change programmes for carers and/or those with ADHD. This section describes the evidence base for pharmaceutical, behavioural and non-mainstream treatments for ADHD.

2.3.1 Pharmaceutical medications

Numbers treated pharmaceutically have outstripped rates of diagnosis, doubling between 2003 and 2008 in the UK (McCarthy, et al., 2012); and increasing nearly 700% between 1990 and 1997 in the US (Doherty, Frankenberger, Fuhrer, & Snider, 2000). Cumulative methylphenidate dosage has increased 92% since the 1960s, 80% since the 1970s, and 56% since the 1980s (Swanson, et al., 2017).

Stimulants such as methylphenidate (trade names Ritalin, Concerta, Equasym, Xenidate, Tranquilin or Medikinet), dexamfetamine and lisdexamfetamine dimesylate, and non-stimulants (atomoxetine and guanfacine) are the main medications prescribed (NICE, 2008). They are available as immediate-release formulations requiring several doses daily, and more recently as once-daily extended-release formulations, which have been found to be better adhered to (Marcus, Wan, Kemner, & Olfson, 2005). Titration of dosage is required to maximise therapeutic benefits and minimise adverse events. The ideal dose for cognitive/academic functioning is considered to be lower than the ideal dose for behavioural functioning (Hale, et al., 2011). Children on higher doses may be better able to sit still and keep quiet, but less able to think acutely, whilst those on lower doses may be better able to think clearly, but less able to behave appropriately in the classroom.

Short-term outcomes

The many randomised controlled trials testing pharmaceutical medication against placebos demonstrate large effect sizes. The most recent meta-analysis of methylphenidate treatment(Storebo, et al., 2015) found it improved teacher-rated ADHD symptoms by a standardised mean difference (SMD) of -0.77 (95% CI -0.90 to -0.64; 19 trials, mean duration 75 days, 1698 participants). The most recent meta-analysis of amphetamine treatment (Punja, et al., 2016) found it improved teacher-rated ADHD symptoms by a SMD of -0.55 (-0.83 to -0.27; 5 studies; 745 children/adolescents); parent ratings by a SMD -0.57 (-0.86 to -0.27; 7 studies; 1247 children/adolescents), and clinician ratings by a SMD -0.84; 95% CI -1.32 to -0.36; 3 studies; 813 children/adolescents).

Both these Cochrane meta-analyses classified the evidence they synthesised as very low quality. Incomplete outcome data resulting from failure to report drop outs was considered problematic by Punja et al. (2016). Storebo et al. considered problematic: the incomplete reporting of results; the high possibility that people knew which treatment the children were taking; the varied results across trials for some outcomes; and the potential for Industry bias (Storebo, et al., 2015).

70-80% of children are found to profit from at least one psychostimulant in the short-term (Markowitz, Straughn, & Patrick, 2003). Pharmaceuticals have a significant short-term impact (> 2 months) on symptoms such as classwork productivity, quality of completed work, number of problems completed on tests, improved quiz scores (Evans, et al., 2001; Pelham, et al., 2001); working memory (Strand, et al., 2012); organization, time management and planning (Abikoff, et al., 2004); aggressiveness (Sinzig, Döpfner, & Lehmkuhl, 2007); handwriting (Tucha & Lange, 2001); gross motor co-ordination, impulsivity, and compliance with requests (Adesman & Wender, 1992).

Pharmaceuticals may not address academic achievement (Corkum, McGonnell, & Schachar, 2010; Langberg & Becker, 2012); antisocial behaviour or arrest rates (Wilens, et al., 2003); or social dysfunction (De Boo & Prins, 2007).

Pharmaceutical management of emotional dysregulation

The impact of pharmaceuticals on emotional dysregulation is less researched and established (Mordre, Groholt, Kjelsberg, Sandstad, & Myhre, 2011). Manos et al. (2011) in their literature review of changes in emotions related to pharmaceuticals found that children have both positive and negative emotional responses. Their evaluation of 47 RCTs measuring emotional regulation found positive effects in two, but the majority of studies noted emotional dysregulation as an adverse event. Shaw, Stringaris, Nigg, & Leibenluft, (2014) found five RCTs of pharmaceuticals in children assessing change in emotion regulation, with mixed results.

NICE consider psychostimulants effective in treating oppositional defiant disorder comorbid with ADHD (NICE, 2008).

Long-term outcomes

The long-term effectiveness of pharmaceutical treatment for ADHD remains in doubt (Tarver, Daley, & Sayal, 2014). Reviews find that poor adherence and persistence, comorbidities and poor follow-up contribute to difficulties in measuring long-term effects and complicate interpretation of results. Where lack of improvement in long-term outcomes is found, it is argued that it is unclear whether this is due to lack of medication adherence, or the inability of medication to influence long-term outcomes. The most recent evidence on long-term outcomes from the Multimodal Treatment of ADHD (MTA) study suggests the latter: naturalistic subgroups based on patterns of medication use (consistent, inconsistent, and negligible) found that extended use of medication did not provide greater symptom-related benefit but did result in reduced growth (Swanson, et al., 2017).

The MTA study is the best-known, most recent and largest comparative study (N=579) of the long-term outcomes of ADHD. It investigated the relative effectiveness of 1) optimum stimulant medication management, 2) behavioural treatment, 3) their combination, and 4) usual or 'community' care (which in the US typically meant pharmaceutical treatment). The primary outcome measure was unblinded carer and teacher symptom ratings.

At 14 months, pharmaceutical management and combined treatment were superior to behavioural treatment or community care (MTA Cooperative Group, 1999). However, benefits dissipated after the 14-month treatment-by-protocol phase. By 36 months any trends had disappeared (Jensen, et al., 2007), and at 8 years participants were significantly worse than a control group on 91% of measures (Molina, et al., 2009). Collection of salivary samples found that only 50% of participants assigned pharmaceuticals were consistently adherent during the 14 months of the trial (Pappadopulos, et al., 2009), and were only on pharmaceuticals for 43 % of the days between baseline and 8-year follow up (Langberg & Becker, 2012).

The reasons why the original differences between groups disappeared has been extensively debated. Arguments range from: the pharmaceutical medication was no longer effective; all participants improved from treatment and improvement was sustained; the natural course of the disorder accounted for the improvement; treatment benefits were only maintained whilst medication management was maintained. The best interpretation may be that the data were confounded and conclusions difficult to draw (Shaw, et al., 2012).

Where pharmaceuticals are adhered to, other studies have suggested that improvements are sustained. One 10-year study found a mean duration of treatment of 6 years, and along-

side fewer disruptive disorders and less school failure (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009). Charach et al. (2004) found that at 2 and 5-year follow-up, adherent participants showed improvement in teacher-reported ADHD symptoms in comparison with non-adherent participants. Hechtman (2004) found that consistently monitored participants whose medication use was actively titrated over a 1–2 year period maintained improvements in ADHD symptoms and academic outcomes.

Systematic reviews of long-term outcomes have found that pharmaceutical treatment of ADHD improves life functioning, self-esteem, social function, core ADHD symptoms and academic performance (Hodgkins, 2012; Arnold, 2015; Harpin, 2016; Parker, 2013; Langberg, 2012). Hodgkins (2011) concluded that pharmaceutical treatment may reduce the negative impact that untreated ADHD has on life functioning but not to the point of normalization. Arnold, from the same team (Arnold, Hodgkins, Caci, Kahle, & Young, 2016) concluded that a combination of pharmaceutical and non-pharmaceutical treatment was most consistently associated with improved long-term outcomes, and that treatment cessation attenuated results. Harpin (2016) found that the majority of self-esteem and social function outcomes were improved. Parker (2013) found that that pharmaceutical and behavioural interventions were effective in managing core ADHD symptoms and academic performance at 14 months, but after that there was little evidence to suggest that the effects are maintained.

Langberg (2012) found long-term pharmaceutical medication use to be associated with improvements of minimal educational or clinical significance: 5 year gains were equivalent to .19 school years for maths and .29 school years for reading (Scheffler, et al., 2009).

Regarding criminality, no systematic review was identified. In one cohort of 126 children, pharmaceutical medication did not reduce offending levels (Langley, et al., 2010). The MTA study concluded that cause-and-effect relationships between pharmaceutical treatment and delinquency are unclear, indeed by 24 and 36 months, more days of prescribed medication were associated with more serious delinquency (Molina, et al., 2007).

In summary, studies suggest that if effective pharmaceutical treatment is maintained, benefits may persist. Negative long-term prognoses are likely due to both lack of persistence with pharmaceutical medication, and its inability to normalise impairments. Those with ADHD continue to be at risk of negative long-term outcomes, and researchers continue to debate the risks and benefits of pharmaceutical treatments (NICE, 2008; Poulton, et al., 2013; Storebo, et al., 2015).

Side effects of pharmaceutical medications

Adverse side effects associated with pharmaceutical medication are common: decreased appetite, sleep disturbance, headache, abdominal pain, nausea and vomiting, depression,

anxiety, emotional outbursts, weight loss, delay in height gain, dizziness and increased blood pressure (Wigal, et al., 2006; Wolraich, McGuinn, & Doffing, 2007; http://www.nhs.uk//Conditions/Attention-deficit-hyperactivity disorder/Pages/Treatment.aspx.)

Children have also been found to be at risk of developing some type of tic (Doherty, Frankenberger, Fuhrer, & Snider, 2000). In the MTA study 64.1 % of children studied suffered from one or more mild, moderate, or severe side effects (MTA Cooperative Group, 1999). In the meta-analysis of methylphenidate treatment children were found to be at 60% greater risk for trouble sleeping/sleep problems, and 266% greater risk for decreased appetite (Storebo, et al., 2015). In the meta-analysis of amphetamine treatment an 85% greater risk for decreased appetite was identified; 59% greater risk for insomnia/trouble sleeping; 13% greater risk of abdominal pain; and 26% greater risk of nausea/vomiting (Punja, et al., 2016).

Serious adverse reactions, such as psychotic symptoms and mood disorders are thought to affect about 3% of children (MTA Cooperative Group, 1999; NICE, 2008; Pliszka, 1998). Sudden death, seizures and suicidal thoughts have also been reported (Vitiello, 2008; McCarthy, Cranswick, Potts, Taylor, & Wong, 2009; Eli Lilly and Company methylphenidate instruction leaflet, 2008).

Reduced growth of 2-4 cm has recently been confirmed in those taking pharmaceutical medication continuously from childhood through adolescence compared to their non-ADHD peers (Swanson, et al., 2017; Poulton, et al., 2013). It is suggested that the effects of stimulants on growth are dose-dependent (Graham, et al., 2011) which may explain why height reduction of treated children was not observed until recently (Biederman, Spencer, Monuteaux, & Faraone, 2010), since cumulative methylphenidate dosage has increased 92% since the 1960s (Swanson, et al., 2017).

According to the carers of children with autism, pharmaceutical medications for ADHD cause more problems than they help (0.6:1 ratio of better: worse (http://www.autism.com/). Children may be more vulnerable to side effects and not experience positive benefits (Ghanizadeh, et al., 2012; Stigler, Desmond, Posey, Wiegand, & McDougle, 2004; Troost, et al., 2006). Those studies which do show the effectiveness of pharmaceutical medication tend to have used high functioning autism samples, tested non-stimulant medication, be small, uncontrolled, and have potential confounders (Posey, et al., 2006; Zeiner, Gjevik, & Weidle, 2011; Arnold, et al., 2006).

Adherence to pharmaceutical medication

The literature suggests a low persistence rate, (as discussed in the section above looking at long-term outcomes), and nonadherence to pharmaceutical medication to be the norm ra-

ther than the exception (Langberg & Becker, 2012). Children in the UK have been found not to take pharmaceutical medication for longer than 6 months (Raman, et al., 2015), and studies in the US concur: 1 in 5 (Froehlich, et al., 2007) and 50% (Perwien, et al., 2004) discontinue after the first prescription, and as discussed above (long-term outcomes) only 50 % of trial participants in the MTA study were adherent to their assigned medication (Pappadopulos, et al., 2009).

Treatment adherence drops significantly in teenagers (McCarthy, et al., 2009), who are found to dislike taking pharmaceutical medication due to its side effects; don't see a need for, or improvement from, medication; and/or dislike the attached social stigma (Brinkman, et al., 2012). Teenagers describe changes in their sense of self which lead them to want to discontinue use (Barbaresi, et al., 2006). According to a review of lack of adherence (Frank, Ozon, Nair, & Othee, 2015), their reasons for discontinuing are: "own wish, remission/don't need (19%); withdrawal of consent (16%), adverse effects (15%) of which the most common is reduction in weight and appetite; and, suboptimal effect (15%).

Concerns regarding pharmaceutical medication

Whilst pharmaceutical medication improves core symptoms and other important outcomes over the short-term, its dominance as a treatment option has always been a cause for concern (Wright, 1997). The NICE guidelines were written in response to this concern according to personal communication with the Director of Guidelines. Carers have ethical concerns about the use of medication (Perring, 1997); unhappiness about using psychotropic medication in children; concerns about side effects and long-term harms; concerns that medication takes away individual responsibility for problems; and unease that the focus of treatment is on the child, not the interface between them and the social and educational systems (NICE, 2008). Concerns are also raised about stimulant drug misuse and diversion (NICE, 2008), although Mannuzza et al., (2008) and Biederman et al., (2008) found early treatment with stimulants did not contribute to later substance abuse.

Other concerns, (also discussed above), are that the strong short-term effects of pharmaceutical medication measured are not sustained. Children do not adhere to their medication regimes, particularly when teenagers. Children may have secondary problems not resolved with pharmaceutical medication (Pelham & Gnagy, 1999) or caused by it (Owens, 2008). Pharmaceutical medication does not usually bring children within the clinically normal range; and a significant number of children (< 25%) fail to respond to it (Markowitz, Straughn, & Patrick, 2003). Furthermore, pharmaceutical medication is commonly associated with side effects such as sleep problems and decreased appetite (Storebo, et al., 2015), and reduced growth (Swanson, et al., 2017).

Pharmaceutical medication costs

In the UK, the annual cost of prescribed pharmaceutical medications to the NHS in 2006 was roughly £29 million, a 20 % increase from the previous year. By 2010 with increased prescription rates the cost to the NHS increased to £43.8 million (NICE, 2013). It is estimated that pharmaceutical medication expenditures for ADHD in the UK will have exceeded £78 million by 2012 (Schlander, 2007) due to growing acceptance and intensity of pharmacotherapy and higher unit costs of medications (NICE, 2008). Initial assessment costs are estimated at £23 million, and follow up care excluding medication, £4 million annually (King, et al., 2006).

The cost-effectiveness of pharmaceutical medication

Treatment cost-effectiveness studies have primarily focused on methylphenidate use in the US, where it is found to be a cost-effective treatment option with ratios ranging from $15,509 to $27,766 per quality-adjusted life year (QALY) gained for short and medium-term benefits (Gilmore & Milne, 2001). In the UK the NICE technical analysis estimated the additional cost per QALY gained for methylphenidate compared to no treatment at £9,200 (£4,700 to £28,200) (Lord & Paisley, 2000). It was concluded that pharmaceutical treatments are cost effective compared to no treatment, but a combination of pharmaceutical medication and psychological therapies are not (King, et al., 2006). Evidence of cost-effectiveness beyond 6 months is poorer due to difficulties in unpicking the effects of pharmaceutical medication and the effects of non-adherence.

Behavioural treatment costs are far higher than pharmaceutical medication costs: the MTA study estimated that at 14 months pharmaceutical medicine costs were $1079 per child, and behavioural treatment costs $7176 (Jensen, et al., 2005). The following section reviews the evidence base for behavioural interventions.

2.3.2 Behavioural change interventions

Behavioural change programmes such as social skills training and cognitive behavioural therapy are recommended as treatment options in the UK (NICE, 2008). Parent training and education programmes aim to teach parents about behaviour management; increase their confidence in their ability to help their child; improve their relationship with their child; improve children's behaviour and peer relationships. They are designed to develop strategies to cope with difficult behaviour secondary to, or coexisting with, ADHD rather than address the core symptoms, and are considered particularly in pre-school years when medication is not licenced.

Cognitive behavioural therapy (CBT) aims to help children (usually adolescents) manage problems by changing the way they think and behave. Social skills training involves children taking part in role play situations, aiming to teach them how to behave in social situations

by learning how their behaviour affects others. In the UK, there are a variety of 'branded' parenting programmes such as *123 Magic* (Bloomfield & Kendall, 2010), *Triple P* (Nowak & Heinrichs, 2008), *Incredible Years* (Webster-Stratton, Jamila Reid, & Stoolmiller, 2008) and *the New Forest Parenting Programme* (NFPP) for pre-school children (Sonuga-Barke, Daley, Thompson, Laver-Bradbury, & Weeks, 2001). In Sheffield, the MAG (Managing ADHD Group) run by Sheffield Family Action is used.

Programmes are usually in groups of 10-12 carers for 10-16 meetings of up to two hours each, but may vary (individual vs. group, session length, duration of treatment). What programmes have in common is the training of carers and/or children in behaviour management techniques using positive reinforcement and rewards to encourage children to try to control their ADHD (The New England Comparative Effectiveness Public Advisory Council, 2012).

Assessment of outcomes for behavioural interventions

Effect sizes in behaviour intervention trials vary as a function of design and comparator: between-group design effect sizes range from 0.03 to 1.31 (median 0.44); within-subject designs from 0.10 to 2.39 (median 0.46); and single-subject case studies, which constitute the majority of the evidence, from 1.07 to 14.35 (median 3.46) (Pelham & Fabiano, 2008).

Policy decision makers such as NICE use between-group studies to inform guidelines (NICE, 2008), whilst advocates of behavioural interventions argue that other designs should be included, since most medication studies are also within-subject short-term crossover studies (Conners, 2002; Fabiano, et al., 2009). Therefore the effectiveness of behavioural interventions is contested. NICE conclude that although there are some gaps in the evidence base, interventions are beneficial, and some have demonstrated improvements in core ADHD symptoms (NICE, 2008). However, Cochrane reviews find little evidence of effectiveness and high risk of bias which compromises findings (Zwi, Jones, Thorgaard, York, & Dennis, 2011; Storebø, et al., 2011).

Outcomes are influenced by: rater status, age, what is measured, what is compared, how long studies are, and what type of trial design is used. How study results are interpreted depends upon opinions about the acceptability of aspects of study designs since behavioural interventions (possibly inevitably) are considered to have poor internal validity, and be at high risk of bias. Whether the quantity of poor quality studies is sufficient to mitigate for their poor quality is questioned (Sonuga-Barke, et al., 2013).

Rater status as a moderator of treatment outcome

Studies tend to find more positive effects when assessments are made by unblinded parents, but not by blinded raters (Sonuga-Barke, et al., 2013). Interpretations for this include: that unblinded raters are biased and overestimate treatment effects; that interventions increase parental tolerance for ADHD or their ability to cope with its negative impact rather than decreasing symptom levels; that blinded measurements are less valid than more proximal measurements; or that intervention effects do not generalize from the therapeutic setting (e.g., the home) to other settings (e.g., school) (Daley, et al., 2014).

Age as a moderator of treatment outcome

Pre-schoolers' carers participate in parenting courses; school age children participate in CBT courses, parenting programmes or family therapy; adults and teenagers participate in CBT based therapies. Age appears to be a moderator of treatment outcome and evidence for effectiveness is stronger for pre-schoolers and adults than school age children.

In the UK, pharmaceutical medication is not licenced for pre-schoolers. In the USA, where it is, evidence suggests behavioural interventions are more effective than methylphenidate in reducing disruptive behaviours and ADHD symptoms (Mulqueen, Bartley, & Bloch, 2015; Charach, et al., 2013). In the UK, The NFPP has been found to increase levels of positive parenting and reduce mental health problems when implemented by motivated and trained health visitors with experience in childhood behaviour problems (Sonuga-Barke, Daley, Thompson, Laver-Bradbury, & Weeks, 2001), but not when delivered in a more standard community setting using non-specialist health visitors (Sonuga-Barke, Thompson, Daley, & Laver-Bradbury, 2004).

In school age children, neither parenting programmes, CBT or family therapy have emerged as being as effective as pharmaceutical medication. Therefore in the interests of cost effectiveness, pharmaceutical medication has increasingly become the predominant treatment. Few well-controlled studies of behavioural interventions for teenagers have been done (Pelham & Fabiano, 2008) and the results of those are equivocal. It is suggested that paucity of studies is because they have not been well received in practice.

In adults, CBT programmes appear to be effective for ADHD symptoms and functioning, and pharmaceutical medication not to offer additional benefits (Weiss, et al., 2012). It is suggested that adults may have obtained greater insight into their difficulties with ADHD and be receptive to learning better ways of coping.

What is measured as a moderator of treatment outcome

Behavioural interventions are generally not considered to decrease the core symptoms of ADHD, but to improve children's functioning in areas not affected by medications, and these

are what tend to be measured. For example, in the MTA study, whilst medication alone significantly decreased core symptoms of ADHD, only children who received behavioural treatment in addition to medication saw significant improvements in child social skills, carer-child relationships, and positive parenting practices (Hinshaw, et al., 2000).

Improvements are found in children's oppositional and aggressive symptoms, parenting, teacher-rated attention, aggression and social skills; observer-rated externalizing problems; behavioural functioning and academic performance; and decreased parental stress (Webster-Stratton, Reid, & Beauchaine, 2011; Langberg, et al., 2010; Williford & Shelton, 2014).

Control conditions as a moderator of treatment outcome

Control conditions are considered to influence results. The majority of behavioural studies are single within-subject designs, comparing effects before and after, and these demonstrate large effect sizes. In school settings such as the MTA study, the control condition was school as usual, where it is suggested that results were confounded since behavioural interventions are ubiquitously used in classroom settings (Gottfredson & Gottfredson, 2001; Walker, Ramsey, & Gresham, 2003). In other studies in controlled classroom settings where naturalistic contingencies were removed, the behaviour of ADHD children was found to deteriorate substantively (Fabiano, et al., 2009), and behavioural treatment effects consequently magnified. Researchers argue that doing this employs a control condition that is comparable to a placebo condition in a drug study, and therefore a more valid comparison of the two treatments (Pelham & Fabiano, 2008).

Behavioural interventions for emotional dysregulation

There is some evidence that behavioural interventions may be helpful for emotional dysregulation. A systematic review of parent training interventions by Zwi et al. (2011) suggests a moderate effect on unblinded measures of internalising behaviours (e.g withdrawal and anxiety) according to two studies; but a non-significant effect on externalising behaviours (rule breaking, oppositional behaviour, aggression) according to three studies. However, the risk of bias was considered high because no studies provided information on randomisation and allocation concealment; and inevitably, blinding of participants, personnel or outcome assessors (who were most often the parents who had delivered the intervention) was impossible.

Chan (2016) in another systematic review of ADHD treatments for adolescents found inconsistent small to medium effects on emotional aspects in adolescents according to five studies. Meta-analysis by Daley et al. (2014) (32 studies) found both blinded (SMD = .31) and unblinded improvements (SMD = .26) in conduct problems.

Adherence to behavioural interventions

Adherence to behavioural interventions can be as problematic as adherence to pharmaceutical medication. Whilst Daley et al. (2013) and Thompson et al. (2009) found that most carers offered a place on a parenting course took it up, Taylor et al. (2015) found attendance to be 31–54 % of those recruited, and Barkley et al. (2000) found that one third of carers attended no classes, and only 13% attended more than half.

Reasons for attrition were found to be: situational (transport, childcare, timing/venue); psychological (low self-confidence, fears of being judged a bad parent, stigma, shame, embarrassment, distrust); perceiving programmes as unhelpful, irrelevant or demanding; poor relationship with the therapist; problems implementing strategies; having an unsupportive family/partner; being a single and/or young carer; the intervention not a priority when faced with multiple challenges; and changes in circumstances (Scott, et al., 2010); (Koerting, et al., 2013).

Concerns regarding behavioural interventions

There are concerns about the sustainability of behavioural interventions, their inability to improve core ADHD symptoms, and the nature of the trials conducted. Gains may only be sustained whilst the behavioural interventions remain in place in the settings and during times when the child experiences difficulties (Barkley, 2006). Most reviews comparing pharmaceutical medication and behaviour change programmes conclude that pharmaceutical medication is more effective than behaviour modification (Hinshaw, 2007; Jadad, Boyle, Cunningham, Kim, & Schachar, 2000).

Despite numerous studies of behavioural interventions, the evidence base is still disputed, largely because improvement tends to be found in unblinded not blinded ratings (NICE (2008), (discussed in greater depth in section 3.1.8). The majority of trials with positive results compare before and after outcomes in the same unblinded subjects. Where trials compare medication with behavioural interventions, the behaviour arm does not appear to show improvements in ADHD symptoms, although does in other functional outcomes. Therefore ADHD experts question the effectiveness and utility of behavioural interventions which are labour intensive and costly. For example, the MTA' s summer treatment programme was conducted for 6–8 hours a day, five days a week, for many weeks (Wells, et al., 2000) and incurred over twice medication costs.

It is of concern that there are few studies of behavioural interventions for teenagers. It is likely that these are not being done because teenagers are not receptive to them since this is a time when many teenagers stop taking pharmaceutical medications, so there is an un-

met treatment need during these years. The absence of acceptable interventions at this stage is likely to be contributing to poor long-term negative outcomes.

2.3.3 Summary – mainstream treatments

This section has interrogated the evidence for improvement of outcomes using mainstream treatments. The bulk of the evidence in support of both pharmaceutical medication and behavioural approaches suggests that whilst implemented, treatments may effectively palliate symptoms, making classroom and family life more manageable for the majority of children with ADHD. Despite these findings, long-term outcomes are not being substantially affected, and a negative prognosis is associated with a diagnosis despite large increases in pharmaceutical medication. This may be because in general, neither intervention type is accessed for long: pharmaceutical medications tend not to be taken for long periods, and behavioural interventions only last for 8 - 12 weeks.

Comparisons of the long-term effectiveness of behavioural interventions and pharmaceutical medication suggest that behavioural interventions are less effective than pharmaceutical medications at improving core ADHD symptoms. However, it is argued that comparisons are biased since in studies, children continue to take pharmaceutical medication, but behavioural interventions are only accessed for limited periods (Pelham & Fabiano, 2008).

Nevertheless behavioural interventions are considered a useful supplement to pharmaceutical medication despite evidence for their effectiveness and ability to effect long-term prognoses being disputed, and their being costly to implement. In the UK, although recommended by NICE (2008), provision is inconsistent and variable with a lack of psychosocial services, assessment and treatment protocols. Neither intervention appears to be particularly acceptable to those with ADHD. This may be an artefact of the condition, or a comment on the interventions, likely both.

Much debate regarding interpretation of the evidence concerns trial design. This issue is discussed in greater depth in Chapter 3, and is seminal to the rationale for this thesis. Trials of medication, which demonstrate strong short-term effects, are accused of not transferring to real-life practice, including benefit/side effect ratios, or measuring long-term effectiveness (Storebo, et al., 2015). Trials of behavioural interventions are accused of being prone to bias as carers supplying assessments are usually directly involved in treatment delivery.

2.3.4 Non-mainstream treatments

ADHD is a highly researched condition. Publications increased from 356 in 1985–89 to 6158 in 2005–9. (Bishop, 2010). But the weight of this weighty evidence does not suggest that mainstream treatments are substantially influencing long-term negative outcomes. There is

a logical argument that resources might be better used exploring different interventions, such as the adjunctive treatments to which carers turn (section 1.5.3).

Currently there is insufficient, inadequate evidence for the non-mainstream treatments they are using. What evidence there is generally takes the form of small, underpowered, poorly designed and reported studies (Whitehouse, 2013). This despite the fact that an estimated 50,000 complementary practitioners work in the UK providing treatment to around 5 million patients a year (Budd & Mills, 2000). In 2000, the House of Lords identified as a public health issue that we do not have adequate knowledge of the putative benefits of these therapies (House of Lords Select Committee on Science and Technology, 2000).

They identified that development of a robust evidence base for these under-researched interventions is restricted by a lack of industry funding, and/or academic researchers to conduct such studies. A programme was put in place to mitigate for this within the Department of Health and ten fellowships ring fenced for the field of Complementary and Alternative Medicine (CAM). However, at the same time a successful campaign was implemented to prevent such potential CAM researchers from obtaining University degrees (which included research modules) in their CAM subjects (Anwar, Jim, Huckbody, & Hughes, 2001). The Department of Health initiative no longer continues, and there continue to be few researchers with an understanding of or interest in CAM.

Non-pharmaceutical treatments for their child's ADHD are found to be preferred over pharmaceutical treatment by carers (Corkum, Rimer, & Schachar, 1999). Reasons include: looking for alternatives to conventional drugs (Baumgaertel, 1999; Brue & Oakland, 2002; Gross-Tsur, Lahad, & Shalev, 2003); minimising symptoms of ADHD; additional benefit when combined with conventional treatment; avoiding side effects of prescribed medication (Sinha & Efron, 2005; Hanson, Kalish, & Bunce, 2007); seeking additional symptom relief; and dissatisfaction with conventional care (Bishop, Yardley, & Lewith, 2007).

CAM are used alongside (complementary) or as a substitute (alternative) to conventional treatments and not routinely used by medical or other health professionals (Hall & Riccio, 2012). The Cochrane collaboration describes CAM as "a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture, defined by their users as preventing or treating illness or promoting health and wellbeing. Boundaries within CAM and between the CAM domain and that of the dominant system are not always sharp or fixed" (Wieland, Manheimer, & Berman, 2011).

The US National Center for Complementary and Integrative Health (NCCIH) divides CAM into three categories: natural products (such as diets and supplements); mind-body practices

(such as yoga, chiropractic and osteopathic manipulation, meditation, and massage therapy); and a third category of approaches which "may not neatly fit into either of these groups" but can be termed holistic or whole medicine systems: ayurvedic medicine, traditional Chinese medicine, homeopathy**,** and naturopathy (https://nccih.nih.gov/health/integrative-health).

This third category takes a whole system or holistic approach suggesting interconnectedness (Koithan, Bell, Niemeyer, & Pincus, 2012) and considers all aspects (mental emotional, physical and general) of the patient as an individual. It has been defined as ''an approach to health care ….. to maximize the patients' capacity to achieve mental and physical balance and restore their own health, using individualised, non-reductionist approaches to diagnosis and treatment'' (Verhoef, et al., 2005). Such holistic interventions which address a global constellation of symptoms (Foisy & Williams, 2011) may have a particular role to play in improving ADHD outcomes due to its heterogeneity and association with co-occurrences. In comparison, pharmaceutical interventions try to eliminate or reduce the impact of a symptom, and outcomes are considered to be linear. Holistic interventions require viewing and testing as a synergistic network.

Prevalence of CAM usage

To identify which non-mainstream treatments were being used by carers, an informal search was made for surveys of CAM use for ADHD using the search terms ADHD, survey, CAM (and specific CAM therapies) in Google Scholar, Web of Science, and cross referencing of any surveys found. No surveys were found documenting CAM use for ADHD in the UK, although a cross-sectional survey of all children in the south-west of England was found which reported that 17.9% under 16 had used some form of CAM.

Nine surveys were found assessing CAM use for ADHD in Australia (n=3), the USA (n=4), Canada (n=1) and Israel (n=1) which are summarised in Table 4. The frequency of CAM use in children with ADHD ranged from 12% to 71%, with lower estimates thought to be the result of comparatively narrower definitions of CAM (Weber & Newmark, 2007; Gross-Tsur, Lahad, & Shalev, 2003). CAM use may also vary depending on nationality since there is consistency across the 3 Australian surveys, although less consistency across the 4 US surveys. CAM appears to be predominantly used alongside stimulant medication use, and this is also described in Table 4 .

There are more surveys regarding the prevalence of CAM use in autism spectrum conditions (ASCs), which show higher and increasing use compared to CAM usage for ADHD. CAM use amongst ASC families in the USA was estimated to be 31% in 2003 (Levy, Mandell, Merhar, Ittenbach, & Pinto-Martin, 2003), 74% in 2007 (Hanson, Kalish, & Bunce, 2007) and 82% in 2013 (Huang, Seshadri, Matthews, & Ostfeld, 2013).

ADHD surveys ask about different CAM therapies: most commonly about dietary interventions (8/9); whilst 4/9 ask about homeopathy and chiropractic/osteopathy; and 3/9 ask about acupuncture, herbs, or yoga. Once the non-mainstream interventions used had been identified from the surveys summarised in Table 4, the evidence base for each intervention was explored. The search strategy was to search Google Scholar, Web of Science and the Cochrane collaboration for peer reviewed meta-analyses, systematic reviews or RCTs (in that order) using the surveyed interventions, plus ADHD as search terms. Searches were conducted in 2014.Table 5 describes the evidence found for the surveyed CAM therapies.

Table 4. Complementary and alternative medicine use according to surveys

Study authors	Venue	No: in survey	CAM use	CAM interventions surveyed	% taking pharmaceutical medication
Stubberfield et al. (1999)	Australia	290	64%	Dietary interventions, chiropractic, optometry, use of coloured glasses, use of any other therapy not specifically listed.	69%
Bussing et al. (2002)	USA	822	12%	Chiropractic, homeopathy, massage, acupuncture, faith healing	n/a
Gross-Tsur et al. (2003)	Israel	120	28%	Diet, homeopathy, acupuncture, biofeedback	80%
(Chan, Rappaport, & Kemper, 2003)	USA	114	54%	Expressive (e.g., sensory integration, occupational therapy, art, music, dance), Dietary manipulation, Special exercises (e.g., yoga, tai chi), Relaxation techniques (e.g., meditation), Prayer, Biofeedback, Chiropractic, Herbal remedies, Massage, Healer, hypnosis	51%
(Concannon & Tang, 2005)	Australia	278	71%	Elimination diet, Fatty acid supplement, Vitamins, Behavioural optometry, herbal medicine, Allergy testing, Chiropractic, Sound therapy, Osteopathy, Acupuncture	66%
(Sinha & Efron, 2005)	Australia	75	67.6%	Naturopathy, Herbal Therapy, Homeopathy, Dietary supplements, Modified diet, neurofeedback, Aromatherapy, Therapeutic Massage, Reiki/therapeutic touch, Special exercise, e.g. yoga, behavioural Optometry, Chiropractic, Kinesiology, Osteopathy, Relaxation tape, Meditation, Magnetic Pillow	92%
Johnston et al. (2005)	Canada	73	50%	Vitamin/naturopathy; diet/supplements; family therapy; neuro-feedback	81%
Huang et al. (2013)	USA	135	19.5%	Dietary supplements, Sensory integration, Facilitated communication, Music therapy, Candida therapy, Gluten casein–free diet, intravenous secretin, Kinesiology, behaviour modification, Vision therapy	98%
(Kemper, Gardiner, & Birdee, 2013)	USA	483	36.2%	Biofeedback, hypnosis, guided imagery, meditation, progressive relaxation, qi gong, stress management classes, tai chi, yoga; dietary supplements; chiropractic/osteopathic, massage; homeopathy, naturopathy, Ayurveda, Curandero, Espiritista, Hierbero, Yerbera, Shaman, Botanica, Native American healer/medicine man, Sobador	n/a

Table 5. Evidence base for CAM therapies being used for ADHD

Therapy	**RCTs**	Source	Unblinded assessment	Blinded assessment	Risk of bias
Dietary - fatty acids	11	Meta-analysis: (Sonuga-Barke, et al., 2013)	Carer/Teacher - SMD=0.21, 95% CI=0.05, 0.36. Z=2.67, p=0.007	Teacher/Carer - SMD=0.16, 95% CI=0.01, 0.31. Z=2.05, p=0.0	Jadad rating 3+. Blinded assessment remained significant when analysis limited to 9 trials with no/low medication SMD=0.17; 95% CI=0.01, 0.34).
Dietary - artificial colours	8	Meta-analysis: (Sonuga-Barke, et al., 2013)	Carer - SMD=0.32, 95% CI=0.06, 0.58. overall effect: Z=2.43, p=0.02	Teacher/Carer – SMD=0.42, 95% CI=0.13, 0.70. Z=2.86, p=0.004	6 trials Jadad rating 3+ (i.e. fair). Restricting to 4 trials with blinded assessment: SMD (0.32) (95% CI=–0.13, 0.77)
Dietary - restrictive elimination	7	Meta-analysis: (Sonuga-Barke, et al., 2013)	Carer/teacher -SMD=1.48, 95% CI=0.35, 2.6. Z=2.55, p=0.01	Teacher/Psychologist –SMD=0.51, 95% CI=–0.02, 1.04. Z=1.90, p=0.06	Jadad rating 3+. Individuals were selected for their food sensitivities. 5/7 had blinded assessments
Neurofeedback	5	Meta-analysis: (Micoulaud Franchi, et al., 2014)	Carer - SMD = −0.49 [−0.74, −0.24],	Teacher - SMD = −0.18 [−0.42, 0.07], *p* = 0.15.	Jadad rating 3+ 4/5 studies. 1 study unblinded
Homeopathic medicines	4	Systematic review: (Heirs & Dean, 2009)	none	Carer (2 studies) -1.56 (CI -3.18, 0.06)	Trial heterogeneity, lack of ecological validity
Meditation therapies	4	Systematic review: Krisanaprakornkit et al. (2010)	Unblinded Teacher MD 2.72, 95% CI -8.49 to 3.05	none	Unclear randomization method, unclear allocation concealment, no blinding, unclear attrition rate
Acupuncture	3	Meta-analysis: (Li, et al., 2011)	Carer - Z=2.19 (P=0.03)	none	unblinded, incomplete outcomes.
Massage	1	RCT: (Khilnani, Field, & Hernandez-Reif, 2003)	participants- happiness F(1, 27) = 5.46, p < .05.	Teachers - hyperactivity (pre-post test), F(1, 28) = 7.92, p < .01	No randomisation description, no comparative statistics
Music Therapy	1	(Rickson, 2006). Pilot study	Teachers - no differences between groups (no further information available)	Residential social workers – no differences between groups	Unclear randomisation, no allocation concealment or blinding

SMD = Standard Mean Difference; CI = Confidence Interval. Jadad ratings assess methodological quality allocating trials scores between zero (very poor) and five (rigorous) (Jadad, et al., 1996)

As can be seen from Table 5, nutritional interventions are the most surveyed and researched, with some evidence (including blinded assessment) for the effectiveness of aspects of nutrition such as supplementation with fatty acids and restrictive elimination diets. Neurofeedback is the next most researched. It has developed within mainstream medicine so is not generally considered CAM. Homeopathic interventions are the next most researched, with 4 RCTs according to a systematic review conducted in 2009. Meditation therapies also have 4 RCTs. The remainder of the surveyed therapies have few or no RCTs. It is clear that the CAM interventions being used are under researched, and the evidence produced generally rated low quality.

The selected treatments

The therapeutic modalities of homeopathy and nutrition were selected to be tested as two non-mainstream interventions being used by families with some promising preliminary evidence. Both interventions can be considered whole medicine or 'holistic', non-specific approaches to health: general health is considered to be improved through either individually tailored nutritional intake, or through stimulation of self-cure by application of individually tailored, matching homeopathic remedies.

The surveys showed that families both buy over the counter (OTC) nutritional supplements and homeopathic remedies, and also go to visit nutritional therapists and homeopaths for their children with ADHD (Table 4). Buying OTC products is more popular, cheaper, and easier to implement than visiting a therapist or implementing a dietary change (Kemper, Gardiner, & Birdee, 2013). In the US, OTC natural products were the most popular CAM health approach, used by 17.7% of the population, whilst special diets were used by 3%. OTC homeopathic products and/or visiting a homeopath was used by about 1.8% of children (2.2% of adults) (Clarke, 2015; Black, 2015).

There are several reasons why visiting a nutritional therapist or homeopath is a better way of knowing whether that therapy might be helpful, rather than self-selection of OTC products. Therapists provide professional, tailored advice about which supplements/remedies might be most suitable, and professional knowledge about the process. Visiting a therapist is costlier than buying OTC products, but self-selection runs the likelihood of wrongly identifying an appropriate remedy/supplement, and of misunderstanding the process, particularly since changes can take a while to occur. A personally tailored approach by a nutritional therapist is recommended since nutritional sensitivities (which can be varied and diverse) are found in some but not all of those with ADHD, (section 5.4.2), and there are concerns about unsupervised dietary changes during crucial growing periods. A personally tailored approach by a homeopath is a key requirement for identification of an appropriate homeopathic remedy (section 4.1.4).

The interventions were therefore termed 'Treatment by Homeopaths' and 'Treatment by Nutritional Therapists'. 'Treatment by a homeopath' consists of a series of potentially therapeutic consultations and provision of individually tailored homeopathic remedies. 'Treatment by a nutritional therapist' also consists of a series of potentially therapeutic consultations; advice about dietary exclusion and inclusion; menu and lifestyle suggestions and support implementing them; and advice about and provision of individually tailored supplements.

Therapists

NHS funded Integrative Medicine includes treatment by homeopaths (who are also doctors) and is available in Bristol, Glasgow and London, although under threat. Homeopathic treatment is further available within the NHS from GPs also trained in homeopathy. However, the majority of treatment is accessed privately from professional homeopaths.

Dietary advice about healthy eating is available from dieticians in some hospitals and GP practices. Nutritional therapy is practiced privately and within the NHS by doctors who have additional training in nutritional, ecological, and/or functional Medicine. But the majority of treatment is also accessed privately from professional nutritional therapists.

2.4 Summary

This chapter has described the diagnosis of ADHD, and the short and long-term impact of a diagnosis on the child, their family and the education, social services and criminal justice systems. The complexity of ADHD, with its sub-types, multiple common co-occurrences and causal pathways, emerges as a complicating issue for diagnosis and mainstream treatment because "clinicians are inevitably categorisers and so categorical diagnostic systems go with the grain of clinical practice" (Sonuga-Barke in NICE, 2008).

The evidence base for both main and non-mainstream interventions being used as treatments for children with ADHD was explored. Long-term evidence for the effectiveness of main and non-mainstream treatments is weak. The evidence suggests that pharmaceutical medication helps symptom control and improves short-term outcomes, but adverse effects on sleep, appetite, and growth are common, and adherence poor. The evidence for behavioural change programmes suggests their adjunctive usefulness in the short-term, although the evidence continues to be disputed due to differing perspectives regarding trial design. There is minimal research into the non-mainstream alternatives carers try, and existing studies are underpowered and of varying quality.

This chapter has demonstrated that there is a need to improve important, long-term outcomes for those with ADHD. It has identified some of the difficulties with generating this

evidence. There is a need for efficient ways of conducting high quality pragmatic, comparative trials to both answer some of the outstanding questions about current mainstream management of ADHD and explore novel approaches that may be helpful.

Two non-mainstream interventions being used by carers were identified. Both approaches can be classified as taking a holistic approach to health by addressing global constellations of symptoms on an individualised basis. It is suggested that such an approach may be useful and particularly appropriate for ADHD. In comparison, mainstream treatment approaches based on diagnostic criteria struggle with ADHD's heterogeneity, and debate continues regarding categorisation.The evidence base for the two non-mainstream interventions selected - treatment by a nutritional therapist and treatment by a homeopath, will be explored in chapters 4 and 5. Before that, in the following chapter, I will describe the rationale for the trial design.

Chapter 3 Research methods

This chapter identifies some key criteria for a trial design to test whether interventions improve outcomes for children with ADHD. It explores the appropriateness of the TwiCs design to match these criteria.

3.1 Explanatory and pragmatic trial designs

Whether to conduct a pragmatic or explanatory trial depends upon the purpose of the trial. In health care, explanatory trials are used to confirm or refute the existence of a particular hypothesised mechanism of action, provide maximal confidence that any effects seen are not due to other factors, and are relevant for regulatory drug approval. They answer the question "does this treatment work under ideal conditions?" (Sackett, 2011), that is in tightly controlled circumstances, minimising the influence of other variables.

Pragmatic trials are deployed in routine circumstances and are more relevant to policy evaluation and health care decisions of providers and patients. They are designed to provide information to enable decision makers to choose among available alternative interventions, and answer the question "does this intervention work under usual conditions?" (Torgerson & Torgerson, 2008). They use real-world treatment protocols, patient and stakeholder centred outcomes, heterogeneous patient samples and real-world comparators. They are less interested in the mechanisms of 'how' interventions work than 'whether' they work (Torgerson & Torgerson, 2008). The premise of pragmatic trials is that if an intervention is safe, effective, cost effective and helpful to patients, its implausibility is secondary to its therapeutic benefit.

Schwartz & Lellouch initially clarified the essential differences between the two approaches 50 years ago (Schwartz & Lelouch, 1967). However, despite arguments for pragmatic trials "if we want more evidence based practice, we need more practice based evidence" (Prasad, et al., 2013), "the lack of pragmatic trials is an important problem for clinicians and health care decision makers" (Tunis, Stryer, & Clancy, 2003), they are still neither widely accepted nor used. The following section explores some reasons why this might be, by exploring the advantages and disadvantages of each approach.

It is usual for explanatory trials to precede pragmatic trials in staged evidence collection, whereby explanatory trials inform the development of effective interventions, and pragmatic trials then evaluate their effectiveness in a real-world setting. Both approaches are important for a full understanding of clinical treatments and their real-life application. However, not only are some interventions unsuited to efficacy testing, but evaluation in real-world

settings rarely occurs. Pragmatic trials make up just 1.2% of clinical trials (Treweek & Zwarenstein, 2009) so information from efficacy trials is used to inform decision making. More than half the interventions used in routine health care are still of unknown effectiveness (BMJ http://clinicalevidence.bmj.com/x/set/static/cms/efficacy-categorisations.html). Pragmatic trials are rarely conducted in psychology departments where the majority of ADHD research is conducted, but are more common in public health departments, where this PhD is situated.

Features of explanatory and pragmatic trials can be presented as polar opposites (see Table 6). However, in reality designs tend not to be dichotomous (i.e either purely pragmatic or purely explanatory), but on a continuum from more to less pragmatic (Loudon, 2015). For example, explanatory trials may be conducted with pragmatic adjustments such as broader inclusion criteria and longer time frames to ensure they reflect the real-world. Pragmatic trials may include evaluation of blinded outcomes, and/or the addition of a blinded arm (for example, of homeopathic remedies or nutritional supplements) into the effectiveness trial design.

Table 6. Explanatory and pragmatic trials: some archetypal features

Explanatory trials	**Pragmatic trials**
Experimental setting	Routine care setting
Evaluate efficacy	Compare effectiveness
More suitable for acute conditions	More suitable for chronic conditions
Placebo-controlled	Not placebo-controlled
Patients blinded to minimise bias	Patients unblinded to maximise synergy
Aim to equalise non-specific effects	Aim to optimise non-specific effects
Standardised treatment, simple interventions	Routine treatment, complex interventions
Practitioner skilled for standard protocol	Practitioner skilled in routine care
Usually short-term follow-up	Often long-term follow-up
High internal validity, lower external	High external validity, lower internal
Low relevance/impact on practice	High relevance/impact on practice
Homogenous group of patients	Heterogeneous groups of patients
May manage with smaller sample sizes	May need larger sample sizes
More commonly used	Less commonly used

(information extracted from MacPherson, 2004)

Both approaches use randomisation, considered the 'gold standard' method for estimating effectiveness (Torgerson & Torgerson, 2008).

3.1.1 Advantages of an explanatory approach

Research demonstrates the impact of expectation on participants and researchers. For example, two systematic reviews conclude that in spite of a limited number of rigorous clinical studies there is considerable evidence that patient expectation influences their health outcomes (Crow, et al., 1999; Mondloch, Cole, & Frank, 2001). Four randomized trials of acupuncture found that patients with high expectations were more likely to report better outcomes than patients with lower expectations (Linde, et al., 2007).

Expectations can influence both within-group changes (from baseline to follow-up) and between-group differences (between verum and placebo): trial participants with positive attitudes towards a tested intervention may measure larger changes than trials in agnostic samples. High expectations can lead to high response rates in placebo control groups making it more difficult to detect additional specific effects. Explanatory approaches have higher internal validity (defined in section 1.5.4), giving greater confidence that the answers obtained are attributable to the specific variable measured, and reducing the potential for biases such as Hawthorne effects (knowledge that participants are in a trial) or ascertainment biases, to influence the outcome.

Using a placebo comparator and blinding helps separate out specific and non-specific effects and ensures that trial results are not simply explained by regression to the mean, natural history of the complaint, attention from a health professional, or participant's belief they feel better because they are taking an active treatment (Foster & Little, 2012).

Further advantages of explanatory designs are that they may avoid differential attrition (unless the treatment has common side effects). They may address performance biases, as participants are less likely to look for another intervention if allocated a control intervention. They guard against a type 1 error, that is concluding an intervention is effective when it is not (Foster & Little, 2012).

Tightly controlled studies reduce statistical variation, and selection of a homogeneous group of patients for whom the treatment is likely to work best, ensures that if there is an effect, it will be seen. Such trials are preferred by NICE, and other referees and funding bodies (Torgerson & Torgerson 2008). They are more common, and better understood.

3.1.2 Disadvantages of an explanatory approach

Explanatory trials are less suited to answer questions about real-world effectiveness and cost effectiveness because results are less generalisable. Studies may have poor external validity (defined in section 1.5.4), in that trial populations may not be broadly representative

because relatively narrow groups of participants are used; and interventions may not resemble those offered in real-life practice.

If tested interventions are dissimilar to treatments received in clinical practice, results may not accurately predict treatments as experienced in real-life. Researchers document concern that explanatory randomised trials are poor predictors of the real-world effectiveness of the interventions they test (Saunders, Byrne, & Guthrie, 2013; Treweek & Zwarenstein, 2009; Travers, Marsh, & Williams, 2007; Rothwell, 2005). It is argued that if studies cannot be extrapolated beyond the trial population and variables, they may not be worth doing (Berk, 2005). Studies tend to test interventions for short amounts of time, which provides unreliable estimates for health care decision makers about long-term effects and ability to improve long-term outcomes.

Further disadvantages of explanatory designs are that outcomes may be less relevant to patients, for example, if surrogate outcomes are used. There may be difficulties in recruitment due to the use of deception. The ecological validity (defined in section 1.5.4) of the intervention tested may be poor, almost inevitably so if that intervention is complex. Explanatory approaches are particularly unsuited to testing complex interventions since components are interrelated and interact. Teasing out and separately testing individual components runs the risk of a type 2 error in these cases, that is not finding an effect where one exists.

3.1.3 Advantages of a pragmatic approach

Pragmatic approaches are offered as a solution to the external validity problem of explanatory trials in that they retain the rigour of randomisation (thus eliminate selection bias) but retain the characteristics of normal clinical practice (Relton, O'Cathain, Nicholl, & Torgerson, 2010). Pragmatic approaches measuring real-world outcomes of interest (such as educational attainment or criminality) in representative populations (such as those with co-diagnoses and/or involved in criminality) over the long-term provide information for stakeholders such as health care purchasers, providers and patients making choices about treatment.

Evaluation of economic impact fits well with pragmatic designs. If the overarching purpose of health care trials is to help the wider population improve their health, pragmatic trials can help facilitate decision-making about whether therapies should be utilised more widely (Torgerson & Torgerson, 2008). They shrink the gap between research and practice (Weitz, 2015), by being more likely to have higher external and ecological validity. That is, they deliver evidence of effectiveness in everyday clinical contexts, so generalise better to normal clinic settings. The current paucity of such trials is considered a problem for health care decision makers (Tunis, Stryer, & Clancy, 2003).

They are a more appropriate trial design where the use of a placebo control to separate specific from non-specific effects is problematic, such as when complex interventions are tested. Indeed pragmatic trials are specifically recommended for complex interventions by advisory bodies such as the MRC (Craig, et al., 2008), who advise testing the effectiveness of complex interventions before unpacking the black box and exploring the efficacy of individual components.

Results can help us understand more about the acceptability of the intervention to patients since intention to treat analysis is used. Patients may be more likely to volunteer for such trials since they will not be asked to agree to the possibility of being offered a placebo treatment. Such approaches also address ethical issues associated with placebo controls in that no sham treatments are offered (Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012).

3.1.4 Disadvantages of a pragmatic approach

Pragmatic approaches have reduced internal validity, being unlikely to use blinding, which is highly problematic since internal validity is considered a pre-requisite to other validities (Torgerson & Torgerson, 2008). The extent to which the therapeutic relationship contributes to any overall benefit remains unknown after a pragmatic trial. The treatment effect is diluted due to the use of ITT analysis (groups are compared as randomized). The actual effect of the intervention is a secondary analysis, and also risks being a diluted estimate, since other non-specific effects experienced in real-life are not controlled, such as patients changing treatments. Treatment may not be maximally effective in patients already taking medications or other interventions.

Pragmatic trials are less suited to answering questions about modes of action because specific variables are not isolated for testing, and it is difficult to ascertain precisely to what results are attributable. Increased resources may be needed for the larger sample sizes required.

3.1.5 Validity

A key consideration when selecting a trial design, briefly mentioned above, and defined in section 1.5.4, is validity. This issue is further explored here, particularly regarding relevance to pragmatic and explanatory trials of interventions for ADHD. Ideally a trial is well balanced in terms of its internal, external and ecological validity, however, in practice there is a trade-off and inevitable tension between these three. For example, there is inevitably some sacrifice of internal validity in a pragmatic trial to achieve greater generalisability; and some sacrifice of external and/or ecological validity to achieve greater internal validity.

Contributors to poor external validity according to the PRECIS tool for assessment of degree of pragmatism (Loudon, 2015) are: eligibility criteria, recruitment, setting, organisation, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis. Contributors to poor internal validity according to the Cochrane tool for assessment of risk of bias, are: selection bias, performance bias, detection bias, attrition bias and reporting bias (Higgins, Gøtzsche, & Jüni, 2011). Contributors to poor ecological validity vary according to the intervention tested.

Systematic reviews generally assess internal validity, but rarely assess external or ecological validity, and if they do, do so as a secondary consideration. There is no similarly well-integrated tool for their assessment. Examples of tools assessing external validity are: (Downs & Black, 1998): PRECIS (Loudon, 2015) and RITES (Wieland, et al., 2017).

Next, I will discuss the different types of validity with relation to ADHD research and the two interventions selected to be tested.

3.1.6 External validity

There will always be problems moving between the group and the individual. A criticism levelled at pragmatic trials is that by having broad inclusion criteria, it is not possible to know specifically to whom results apply (Torgerson & Torgerson, 2008). However, conducting sub-group analyses can address this, and it is arguably a greater problem that interventions are not tested on populations that they are then applied to. For example, the most common exclusion criteria in trials of methylphenidate (according to data extracted from the appendix of the most recent Cochrane meta-analysis of the benefits and harms of methylphenidate) (Storebo, et al., 2015) are tic disorders, autism, low IQ, anxiety, and a history of substance abuse. But it is common for those with ADHD to have psychiatric disorders (Schmidt & Petermann, 2009), autism (Gillberg, et al., 2004); and tics (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). Storebo, (2015) found that 16/38 parallel group and 14/147 cross-over trials excluded children and adolescents with any other co-occurring diagnosis, despite at least 40% of those with ADHD having co-occurring diagnoses (section 2.1.2).

Ensuring representative participants in trials of interventions for ADHD where we want the results to be generalizable, requires as broad a representation of the condition as possible. This means representation within all the troublesome spheres where ADHD manifests, such as the criminal justice system, special schools, social work and all social strata. It also means allowance of any co-occurring diagnoses. Effort may be required to ensure that breadth of condition is represented: for example, specifically trying to recruit hard to reach, at risk populations.

Setting and organisation can contribute to poor external validity. Consent procedures for trials may be onerous and daunting, and contribute to recruitment difficulties per se, as well as not recruiting representative populations. Failure to recruit is an identified problem. For example, the Shire study (Peasgood, et al., 2016) planned 1,000 and recruited 450. My case series (described in section 4.3), recruited all intervention participants but only 50% of planned control participants. An ongoing RCT (Brulé, 2016) has had to double expected recruitment time. Simple consent procedures mirroring real-life health care may improve recruitment of those most in need but not generally engaged with services or research.

3.1.7 Ecological validity

The ecological validity of interventions is prioritised when a pragmatic design is used. Ecological validity has historically been a particular problem for CAM research: trials attempt to measure the effects of an 'active' ingredient by isolating variables and not acknowledging their interactiveness.

For the therapeutic modality of homeopathy to be applied according to its core principles, it needs to include the principles of the potentiation, similitude and individualisation (section 4.1.4) (Relton, O'Cathain, & Thomas, 2008). The majority of homeopathy trials (217/267, 82.5%) are placebo-controlled, testing the efficacy of standardised homeopathic products, without applying core principles. Just 5.3 % (14/267) test the effects of homeopathic treatment in clinical practice (Mathie, Hacke, Clausen, Nicolai, & Riley, 2013).

For a rounded nutritional approach to be applied, all the identified influential elements of that approach need to be present, such as dietary inclusion, exclusion and supplementation. To date, trials have assessed elements of nutrition separately, assessing exclusion diets, inclusion diets, and individual or multi-nutrients. Researchers agree that separately these cannot address the nutritional issues associated with those with ADHD (Chapter 5).

3.1.8 Internal validity

Randomisation is a core contributor to internal validity since it ensures any allocation biases are eliminated at baseline by unbiased selection of participants to each group based on chance, with potential confounders randomly distributed across groups. Whilst a limitation of randomisation is that it is based on probability, so it cannot be assumed that groups will be similar, it is considered one of the most powerful research tools (Torgerson & Torgerson, 2008). RCTs are considered the best study designs by NICE although in their absence, internally/externally controlled before and after trials, and interrupted time–series may also be considered (NICE, 2008). Studies such as my comparative case series (Fibert, Relton, Heirs, & Bowden, 2016), where groups were allocated consecutively, are considered at risk of bias.

Pragmatic trials are at risk of performance and detection biases since knowledge of allocated interventions by participants and some personnel is inevitable when blinding, sham comparators or placebos are not used. Whilst Higgins states that "it would not be reasonable to consider the trial as low quality because of the absence of blinding" (Higgins, Gøtzsche, & Jüni, 2011), nonetheless, they routinely are.

Expectation bias is an issue when measuring carer-rated outcomes, as frequently occurs in non-pharmacological ADHD research. Carers may inevitably know the intervention status of their child and outcomes influenced by their knowledge of, and involvement in that intervention. Expectation bias can be addressed in a variety of ways: questionnaires can ascertain carers' expectations of treatment; outcomes may be measured by a different assessor who is blind to treatment status (such as a teacher or other health professional); objective outcomes such criminality, school attendance and/or disruption and associated costs, not subject to observation biases can be measured. Hawthorne effects - knowledge that participants are in a trial - may also modify behaviour and contribute to reduced internal validity.

In ADHD research, debate surrounds the blinded and unblinded collection of outcomes. For example, it was found that non-pharmaceutical intervention results are strongly influenced by whether outcomes were blinded, leading to the conclusion that unblinded assessments may be inflated because raters have an investment in treatment success because the carers supplying assessments were directly involved in treatment delivery (Sonuga-Barke, et al., 2013). However, there are also difficulties with using blinded teacher reports: they are difficult to procure because of teachers' workloads; multiple teachers work with the same student; teachers may not observe subtle behaviour changes in large classrooms; some behaviours may be inhibited in classrooms; and school holidays (Biederman, Faraone, Monuteaux, & Grossbard, 2004).

An emerging viewpoint is that reliance on blinded outcomes only gives a partial view of the value of health care, and that the impact of health on wellbeing should also be measured, by asking patients themselves. Patient reported outcome measures (PROMs) are being suggested to become the new currency for comparative assessment of clinical care by European decision makers (Coulter, 2017). There are however, some problems associated with asking ADHD children directly, which are discussed in section 3.4.5.

Resentful demoralisation may occur when participants have a strong preference for an intervention and/or are allocated an intervention they didn't want, therefore provision of equally attractive alternatives is aimed at. Treatment by homeopaths is likely to be a less attractive option than treatment by nutritional therapists due to its reduced acceptability.

High rates of loss to follow up, attrition and non-adherence are contributors to dilution of

the treatment effect and an important source of bias. These are likely to be higher in pragmatic trials due to less tight control,and broader inclusion criteria. There may be a specific issue in ADHD populations where attrition from studies occurs, and chaotic parenting and lack of long-term planning and commitment can be a feature. Larger sample sizes may be required to compensate for this.

3.1.9 Therapist effects

When assessing the effectiveness of treatment by therapists any effects found may parsimoniously be attributed to the therapist rather than the therapy. A personal discussion with the Director of Guidelines at NICE revealed a preference for drug treatments because of confidence that the results obtained in placebo-controlled trials pertained to the action of the tested drug and not the therapist delivering it. He was also concerned with the reproducibility of interventions delivered by therapists. This section discusses some possible analysis and design strategies to address this concern.

Explanatory trials control for therapist effects, but pragmatic trials do not necessarily. The concern is that outcomes may be clustered according to therapist which can lead to inflated standard errors, *p*-values, wider confidence intervals, reduction in the effective sample size, and reduction in the power of the study.

Potential strategies to manage this are to perform cluster level analysis comparing the mean outcome per cluster; use a random effects approach; use a population-averaged approach with coefficients estimated using generalised estimating equations (GEEs); or ignore the clustering and use statistical methods and models that assume the outcomes are independent (Walters, 2010). Walter's comparison of these approaches found little difference between the estimates of the regression coefficients for the treatment effect and confidence intervals for the continuous outcomes. Therefore suggests that the marginal model (that is the average difference in treatment effect between intervention and control groups) should be chosen as this best answers the research question.

However sub-group analysis of participants nested within therapists, using a random effects approach would also be useful, but this requires larger sample sizes, which needs taking into account for power calculation. Treatment by a homeopath and treatment by a nutritional therapist are both therapist led interventions. Because therapist effects are an issue for NICE, I will now explore some possible design solutions. In my case series homeopathic treatment was compared with similar time and attention (Fibert, Relton, Heirs, & Bowden, 2016). I visited control families and had an empathetic chat with them of a similar duration to the homeopathic consultations. Another solution is to conduct multiple trials of therapist

led interventions using the same population and trial design. In this way, therapist effects are held constant.

A third solution might be to use multiple therapists, and/or to randomly select them from a pool of therapists, which can reduce the influence of individual therapists on the outcome (MacPherson, 2004) and address the concern with reproducibility. Describing the intervention and its components using checklists such as those created by Mohler et al. (2012), and Hoffmann et al. (2014) can also be helpful. Checklists include the name of the intervention; the rationale of essential elements; the materials, training and venue; the procedures used and who provided them (expertise, background, and training); the mode of delivery (individual or group); the location; the number of sessions, over what period of time, schedule, duration, intensity, or dose; any individual tailoring (what, why, when, and how); any modifications during the course of the study; levels of adherence (how and by whom, and any strategies to maintain or improve fidelity); and finally, the extent to which the intervention was delivered as planned.

3.1.10 Explanatory and pragmatic trials of interventions for ADHD

The status of ADHD pharmaceutical medication trials mirrors that of trials in general, in that we have substantial explanatory information about the efficacy of pharmaceutical interventions for children with ADHD, but lack sufficient information about their real-life application. In the absence of pragmatic trials, evidence from the explanatory trials dominates evaluations and decision making: almost all trials of methylphenidate compare it to a placebo and are less than six months duration (average duration 75 days) (Storebo, et al., 2015). Reliance on such trials is likely to be affecting the quality of decision making, for example by selection of an intervention lacking evidence of long-term effectiveness, and non-selection of interventions that can't be tested using explanatory designs.

Comparing the evidence for the effectiveness of the two types of mainstream intervention used to treat ADHD to improve long-term outcomes is difficult: drug trials tend to be tested in tightly controlled conditions, and compared to placebos, whereas trials of behaviour change programmes tend to be tested as experienced in practice, and compared to usual care. This means the two types of trials are more/less tightly controlled, have more/less potential for bias, higher/lower expected effect sizes, and answer different research questions (section 2.3).

Assessing the effectiveness of the two non-mainstream interventions selected to be tested is also difficult. What RCT evidence there is compares aspects of the interventions, for example, a homeopathic remedy, or a nutritional supplement, with placebos. This information is unhelpful to stakeholders wanting to know if interventions improve outcomes because:

the homeopathic remedy should ideally be individually tailored; and it is unlikely that any one nutrient is a panacea.

Treatment by a homeopath and treatment by a nutritional therapist are both delivered by therapists. Both conduct consultations of similar duration and provide pills (supplements or homeopathic remedies) to be taken in between consultations. Therefore, several variables which may parsimoniously considered the 'active' ingredient (the time and attention of an empathetic therapist; ingestion of a pill), are held constant across the two therapies. A big difference is that the two interventions are not similarly acceptable, since homeopathy as a therapeutic system is largely discredited in the UK, whilst a nutritional approach is gaining credence and already recommended by NICE.

3.1.11 Comparing explanatory and pragmatic approaches in ADHD research

The current system is inefficient, with trials conducted separately, one at a time, at great expense, providing information to stakeholders which may not translate into real-life. Because trials are conducted in different, often unrepresentative research populations it is difficult to be confident that results pertain to all those with ADHD.

There are difficulties comparing the effectiveness of the two types of mainstream interventions used because the levels of evidence generated are dissimilar. The level of control exerted in a study influences the magnitude of the effect (Gold, et al., 2017). Pragmatic trial results are likely to be compared unfavourably with explanatory trial results. Pragmatic trials are likely to measure diluted specific treatment effects, and exert less control, so the effect size is less than in an explanatory trial.

On the other hand, it is common to see a falling off of effect in clinical practice of the results of explanatory trials, which suggests that effect sizes in more explanatory trials may be inflated compared to their effect in clinical practice. It may be that the evidence generated is the same, but the difference measured concerns the degree of pragmatism of the trial design. This situation is pertinent to the two main interventions for ADHD: behavioural (tested using pragmatic designs) and pharmaceutical (tested using explanatory designs).

Whilst both explanatory and pragmatic trials have a role to play in the development of evidence based interventions, the lack of pragmatic trials is concerning, and information from such trials needed. A further benefit of pragmatic designs is that they measure the acceptability of the offer of the intervention because they use Intention To Treat analysis. This information can be particularly useful for stakeholders making treatment decisions for those with ADHD, since children and their families can be hard to engage, treat, and retain; evidence suggests current interventions are not complied with long-term; and interpretation of results is therefore complicated.

In the next selection I will describe the potential of the TwiCs approach to address some of these issues.

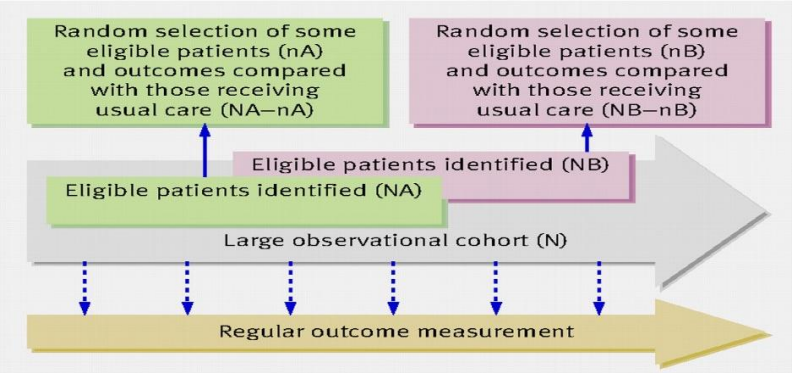
3.2 The TwiCs design

3.2.1 Description of the design

The TwiCs design was outlined in section 1.1. Its essential features and novelty are described below, using diagrammatic and explanatory information extracted from the introductory paper by Relton, O'Cathain, Nicholl, & Torgerson (2010).

The 'cohort multiple randomised controlled trial' design, now known as 'Trials within Cohorts' (TwiCs), firstly recruits a large observational cohort of patients with the condition of interest (N) (Figure 1) and regularly measures their outcomes. For each randomised controlled trial, information from the cohort is used to identify all eligible patients (NA). Some eligible patients (nA) are randomly selected and offered the trial intervention. The outcomes of these randomly selected patients (nA) are then compared with the outcomes of eligible patients not randomly selected; that is, those receiving usual care (NA − nA). This process can be repeated for further randomised controlled trials (for example, NB).

Figure 1. The cohort multiple randomised controlled trial design (Relton, O'Cathain, Nicholl, & Torgerson, 2010)



The design has several innovative features: recruitment of an observational cohort of patients to be used as a multiple trials facility; random selection of some rather than all participants; and patient centred information and consent procedures. It is best suited to trials where treatment as usual is compared with the offer of treatment; outcomes can be easily measured and collected; and conditions where many trials will be conducted.

3.2.2 Use of TwiCs

TwiCs methodology was piloted in the homeopathic treatment of menopausal women (Relton, 2009) and is currently being used in multiple funded trials and studies

(https://www.TwiCs.global/). Cohorts have been set up for conditions such as cancer, scleroderma, lower back pain, mesothelioma, depression and HIV. Non-condition-specific cohorts have been set up in populations such as those born in Bradford, living in Yorkshire, and attending Toronto SickKids hospital. Cohorts of specific at-risk populations have been set up such as the offspring of those with severe mental illness, those attending hospital with violence related injuries, those with skull deformation, the elderly, and those using drugs. A wide variety of interventions are being trialled in these cohorts, such as: podiatry to prevent falls in the elderly; stereotactic body radiotherapy for those with spinal metastases; exercise for those recovering from breast cancer treatment; and parenting courses for those with severe mental illnesses.

It has grown quite fast in the field of clinical research into the effectiveness of homeopathic treatment. Its effectiveness in three clinical areas has been tested: Irritable Bowel Syndrome conducted within the IBS cohort at Barnsley NHS Foundation Trust Hospital (Peckham, et al., 2014); long-term depression, conducted within the South Yorkshire Cohort (Viksveen, Relton, & Nicholl, 2017); and menopausal hot flushes (Relton, O'Cathain, & Nicholl, 2012), where the cohort was specifically recruited. It has thus far not been utilised for research into nutritional interventions or ADHD.

Use of TwiCs for children

TwiCs methodology is being used in several studies aiming to improve long-term outcomes in cohorts of children in Canada, the Netherlands and the UK. There are four studies using the TwiCs design in Canada, with trials being conducted testing whether interventions reduce long-term negative outcomes. FORBOW (Families Overcoming Risks and Building Opportunities) recruits a cohort of offspring of parents with severe mental illness and aims to test multiple interventions to reduce their risk of developing mood or psychotic disorders (Uher, et al., 2014). The CEDAR Project is recruiting a cohort of young indigenous people who use drugs in Canada and testing the impact of mHealth (health care via mobile phones) to see if it reduces their risk of developing HIV.

TARGet Kids! (The Applied Research Group for Kids) is the third Canadian cohort of children. It enrols children aged 0-5 years who visit the SickKids Hospital in Toronto, with the aim of linking early life exposures to health problems including obesity, micronutrient deficiencies, and developmental problems by conducting research within the cohort (http://www.targetkids.ca/our-research). TARget started off as an observational study and conducted several trials using standard approaches to informed consent. It is now converting the cohort so studies can be conducted using a TwiCs approach, and is in the process of receiving approval for the first trial testing full fat or semi-skimmed milk to prevent obesity.

The fourth Canadian cohort is a cohort of youth visiting the emergency Department of Manitoba hospital in Alberta, Canada with a violence related injury, which is a particular problem in this province. Youth are recruited to the cohort on admission, and then randomised to a trial of intensive, wraparound care, initiated at the time of their visit, whilst the control arm receive standard care.

HEADS (HElmet therapy Assessment in infants with Deformed Skulls) is a cohort of children with skull deformation in the Netherlands. An RCT embedded within the cohort is testing the effectiveness of Helmet therapy (van Wijk, Boere-Boonekamp, Groothuis-Oudshoorn, an Vlimmeren, & Jzerman, 2012).

BIBBS (Born in Bradford Better Start Study) has received £49 million in Big Lottery funding to recruit 5,000 babies, and their mothers, and mother's partners, living in Bradford, and implement 22 interventions for children aged 0-3, aimed at improving health and social outcomes in social and emotional development; communication and language development; and nutrition and obesity (Dickerson, et al., 2016).

Ethical approval for TwiCs

Patients, clinicians and NHS Research Ethics Committees have found the TwiCs design to be acceptable: key findings from an international symposium on the ethics of the design (Relton, et al., 2017) were that it is possible to make the case to ethics committees that TwiCs designs are appropriate and ethical. Some bioethicists argue that the design may indeed be ethically superior to previous post-randomization consent designs and can have important advantages over traditional trial designs (Kim, Flory, & Relton, 2017).

3.2.3 Differences between TwiCs and standard designs

The design differs in terms of recruitment, capacity for multiple trials and the process of obtaining consents. Recruitment procedures are different in that participants are initially recruited to a cohort where they are generally not told about treatments they might not receive, or that any treatment they are offered was allocated by chance.

The process of obtaining patient information and consent aims to replicate that in real-world routine health care rather than address the needs of trial design. All cohort patients consent to provide observational data at the outset; however, consent to try a particular intervention is sought only from those offered that intervention. This replicates routine health care where clinicians provide patients with the information they need at the time they need it. (Relton, O'Cathain, Nicholl, & Torgerson, 2010). This attempts to tackle issues associated with standard designs such as those outlined in section 3.1.8. For example, patients not randomly selected act as a virtual treatment as usual (TAU) control group, so are

not aware of having missed out, which addresses the issue of resentful demoralisation. The capacity for multiple randomised controlled trials over time using patients from the same cohort is unique to the design.

3.2.4 Advantages of the TwiCs design

The TwiCs design has the potential for multiple trials which can be conducted long after this PhD is completed, providing ongoing, objective information to stakeholders. Long-term outcomes are collected as standard which can provide ongoing information about the natural history of the condition and usual care, as well as increased comparability between each trial conducted within the cohort. This is an improvement over trials conducted using current randomised controlled trial designs, which trial interventions one at a time and struggle to compare them. All treatments have the same 'treatment as usual' comparator and assess the same core outcomes. As such it has the potential to answer important outstanding questions about the long-term effectiveness of current interventions for ADHD, as well as provide preliminary evidence about the non-mainstream interventions tried by carers. Furthermore, when a variety of interventions are compared using the same design, biases such as Hawthorne effects, expectation and other biases are equally distributed across groups.

A further advantage is its combination of robust design and pragmatism, providing robust evidence which clinicians can apply to their usual clinical populations. Running multiple trials is relatively cheap once the cohort is set up, and multiple interventions can be compared cheaply and efficiently according to similar criteria. Unequal randomisation with larger numbers in the usual care group can enable adequately powered trials to be run more cheaply by saving on treatment costs.

Recruitment may be increased since those recruiting to the cohort have no further expectations. The potential for reporting bias may be reduced when using TwiCs methodology in comparison with other pragmatic RCT designs, because control participants do not know that they serve as control participants. Reporting biases can only occur in the experimental arm (van der Velden, et al., 2017).

It has already been demonstrated that the TwiCs design is suitable for capturing the effects of homeopathy. Furthermore, data on treatment refusers provides information on the acceptability of treatments and thus the generalisability of the trial results.

3.2.5 Disadvantages of the design

Only participants allocated to the intervention arm are asked for informed consent, which happens after they have been randomised to the intervention. An identified problem is that

these participants may then refuse the intervention being trialled, resulting in crossover from the treatment to the usual care arm, and dilution of any treatment effects due to the use of ITT analysis. The proportion of non-compliance in the experimental arm is expected to be higher in the TwiCs design compared with traditional RCT designs (van der Velden, et al., 2017). This may particularly affect trials testing unpopular, time-consuming or inconvenient interventions.

All the criticisms levelled at pragmatic designs discussed in section 3.1.4 pertain to the use of the TwiCs design.

3.3 The suitability of the TwiCs design to test the effectiveness of interventions to improve outcomes for those with ADHD

I have identified that a pragmatic (v explanatory) trial of effectiveness (v efficacy) measuring real-world outcomes of interest (v surrogate markers, or just ADHD symptoms) is required, to test whether interventions improve outcomes for children with ADHD, and evaluate whether they provide a cost-effective way to augment incomplete symptom relief, improve long-term negative outcomes, and inform decision makers.

Due to the range of potential treatments being used for ADHD, there is a need for multiple trials which can be cheaply and efficiently performed. Such trials must be capable of testing and comparing any type of treatment as experienced in the real-world, such as therapist led, whole system, and/or complex interventions as well as pharmaceutical drug treatments.

The TwiCs design fulfils these key requirements, which are discussed in more depth below.

3.3.1 A trial design suitable to test multiple interventions.

Aggregation of data from clinical trials of different therapeutic approaches plays an important role in clinical decision making, treatment guidelines, and health policy. Trial design, comparator choice and degree of pragmatism all influence the levels of evidence generated (Gold, et al., 2017). Comparing designs which generate similar levels of evidence, are similarly pragmatic, and share the same comparator, allows different therapeutic approaches to be more easily compared. Conversely, as occurs currently, and as described in section 3.1, comparing interventions via studies generating different types and therefore levels of evidence leads to the risk of type 2 errors (failure to detect an effect that is present).

A design which tests multiple interventions keeping levels of control and other design features the same across studies can provide useful comparative information to stakeholders. There is an unmet need for research exploring the long-term outcomes of those with ADHD.

TwiCs methodology is demonstrating that it can usefully be employed in cohorts of children at risk of negative outcomes, and embed preventative intervention trials.

3.3.2 A design suitable to test the effectiveness of any kind of treatment

Designs need to be suitable to assess the effectiveness of single element interventions such as drugs and supplements, and therapist led interventions such as behavioural programmes and holistic interventions, since these characterise both conventional and unconventional approaches being used by families.

Interventions with interacting components are difficult to blind, standardise, reproduce and assess. The network of key components of the intervention must be represented; interventions tailored to patient's individual needs can only be standardised to a limited extent; practitioners, participants or families (who are often assessors) cannot be blinded because they are essentially involved in delivery; and reproduction may be difficult because not only are interventions individually tailored, they are also influenced by practitioner expertise. Testing them as experienced in the real-world mitigates for these problems.

The only way to objectively compare different types of interventions such as pharmaceutical, behavioural, and/or holistic interventions, is to compare their effectiveness in real-world clinical practice. A design suitable to assess the efficacy of pharmaceutical medications is not suitable to assess the efficacy of most other interventions. But a pragmatic design can test the effectiveness of any kind of intervention as experienced in clinical practice.

For example, most trials of pharmaceutical drugs control for the impact of many non-specific factors: by using identical placebo treatment comparators; blinding participants, physicians and investigators; having tight inclusion/exclusion criteria; and testing over short time spans which reduces attrition, regression to the mean, and the effects of life events.

Behavioural intervention trials by comparison cannot easily control for the impact of these factors, and both intervention and comparator groups are more likely to be influenced by extraneous variables. They cannot use placebo comparisons, cannot blind participants or physicians, nor can they test over short time periods (since interventions take at least 8 weeks to administer). Trials of behavioural interventions instead try to measure the efficacy of their interventions by controlling factors such as: clinician expertise, programme fidelity, exclusion of participants unlikely to benefit, managing child behavioural and developmental factors, and maternal and demographic factors (Daley & O'Brian, 2013).

3.3.3 A trial design suitable to assess the effectiveness of treatment in real-world populations

Stakeholders need to know how effective interventions might be for real-world populations: families need to know whether it is worth their while investing their time and resources on them; commissioners need trials with real-world populations, including those generating negative outcomes, to decide whether treatments are worth commissioning.

Trials run in reduced populations are likely to be unrepresentative of clinical populations, thus excluding many of those who will use the intervention. Those excluded are often those most in need, such as substance users and those with low IQs. If a design is to assess whether outcomes can be improved, it needs to specifically include rather than exclude those with these co-occurring diagnoses, where helpful interventions are most needed.

Pragmatic trials with their broad inclusion criteria can provide information about whether efficacious interventions for children with single ADHD diagnoses are effective in populations with additional co-occurring diagnoses.

3.3.4 A trial design which can identify and measure real-world outcomes of interest to stakeholders

Improving long-term negative outcomes is a fundamental driver of this research, which aims to provide useful evidence to inform real-world decision making by the variety of stakeholders involved in the management of ADHD. This compares with the measurement of specific effects or surrogate outcomes which informs understanding of mechanisms. Neither public health stakeholders nor patients are primarily interested in the efficacy of different components, their mechanism of action, or the amount of change due to the patient/therapist relationship. They are more interested in whether interventions might augment incomplete symptom relief and improve outcomes. As such measurement of outcomes of importance to policy makers, such as criminality and educational performance are needed. Selection of appropriate outcomes is considered later in this chapter.

3.3.5 A trial design needs to be acceptable to stakeholders.

For this research to be useful, I have argued that it needs to be acceptable to NICE, the national clinical stakeholder because families of those with ADHD tend to access help via the NHS. Local authority decision makers also rely on NHS clinicians' guidance. NICE assesses which treatments produce sufficient benefit that the NHS should pay for them. Guidelines are advisory and do not have legal force but are very influential (Taylor, 2008).

The 2008 Guidelines are currently being updated, for publication in 2018. To understand how guidelines are devised, I read the NICE ADHD clinical practice guideline(NICE, 2008); attended the NICE ADHD clinical guideline update workshop on Nutrition (Hopkins, 2015); and the ADHD stakeholder workshop to inform the guideline update (www.nice.org.uk/.../documents/workshop-notes-2). I also attended several meetings with Dr Gillian Leng, Deputy Director of NICE, and Professor Mark Baker, Director of Clinical Guidelines.

Clinical practice guidelines (CPGs), are developed by development groups, using GRADE criteria (Grades of Recommendation, Assessment, Development and Evaluation) (Higgins & Deeks, 2011). Clinical questions are initially identified by the CPG development group, and then the best design to answer each question is identified (NICE, 2008). It is therefore not possible for a researcher to determine a priori what a question might be and then design a trial to meet requirements.

Evidence may be excluded if a trial does not fit the criteria. For example, in the guideline update for dietary interventions, comparisons between dietary and pharmaceutical or psychological interventions were not permitted (Hopkins, 2015). The majority of studies of elimination diets were excluded because they were either conducted in the incorrect population, used an incorrect comparator, an incorrect study design, lasted under 2 weeks, or were not in English. This left just two studies by a single author (Pelsser, Buitelaar, & Savelkoul, 2009) for consideration.

About GRADE

GRADE considers within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. Four levels of quality are possible, with ratings downgraded depending on: limitations in design and implementation (lack of allocation concealment, blinding, large loss to follow-up, trials stopped early for benefit, selective reporting of outcomes); indirectness of evidence (indirect population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results (studies yield widely differing estimates of effect); imprecision of results (wide confidence intervals, studies include few participants and few events); or high probability of publication bias (investigators fail to report studies or outcomes that show no effect).

GRADE assessments can be interpreted differently with emphasis put on different aspects, exemplified by GRADE assessments in three meta-analyses of methylphenidate for ADHD (Punja, et al., 2016) (Storebo, et al., 2015) (National Institute for Health and Care Excellence (NICE), 2008). Punja graded the evidence low to very low, with studies downgraded if: > 50% of studies had a high risk of bias; the outcome included comparisons of different ampheta-

mine derivatives and release formulations, had significant statistical heterogeneity (I^2 > 50%), or wide confidence intervals.
Storebo also graded the evidence very low, but because it was possible for people to know which treatment children took, reporting of results was incomplete, or some outcomes varied across trials.
NICE graded the evidence moderate to low because studies were short, inclusion and exclusion of co-existing conditions not made explicit, most studies compared drugs with placebos, and adverse events were reported infrequently and poorly. These three analyses demonstrate that despite the aim of objectivity and clarity in assessment of the evidence, results are still subject to interpretation. Largely similar conclusions regarding the levels of evidence were reached, but for different reasons.

NICE guidelines for ADHD

NICE considers that best available evidence should take account of clinical and cost effectiveness and the patient perspective. Outcomes can be: quality of life, ADHD symptoms, cognitive outcomes, functional status, mental health, peer relationships, academic outcomes, family relationships, self-esteem, care needs, safety, and perceived control of symptoms. Comparators can be waiting list, no treatment, usual care, or a placebo intervention. Studies can be RCTs and systematic reviews, and interventions needed to have a GRADE default minimally important difference of -0.5/0.5 standard deviations for continuous outcomes.

Cost effective interventions are those offering health gains per £ spent compared to the best alternative, calculated by estimating the ratio between the cost of the intervention (expressed in £'s) and the benefit produced in terms of years lived in full health (expressed in Quality Adjusted Life Years (QALYs). NICE's 'threshold,' over which treatments are less likely to be recommended, is between £20,000 and £30,000 per QALY. There was no description in the guidelines of how the patient perspective should be taken into account.

3.4 Outcome Measurement

This is an outcome focussed research study. The research question asks how outcomes might be improved for those with ADHD, with the emphasis on improving outcomes (not on the efficacy of interventions). Identifying important outcomes and how to measure them is the topic of this section. Acceptable measures to NICE (section 1.5.3, NICE, 2008) are quality of life, ADHD symptoms, cognitive outcomes, functional status, mental health, peer relationships, academic outcomes, family relationships, self-esteem, care needs, safety, and perceived control of symptoms.

When using the TwiCs methodology, measurement needs to be as un-burdensome as possible, via easy and quick to complete questionnaires collecting important information simply and efficiently.

Outcome measures need to be appropriate to measure change from four perspectives: (1) that of the condition being tested; (2) that of the intervention being tested; (3) that of those most affected by the condition (the child and his/her family); and (4) that of public health stakeholders and decision makers. That means (1) measuring core ADHD symptoms; (2) ensuring measurements are sensitive and broad enough to capture changes by the non-specific interventions selected; (3) identifying outcomes of interest to those affected by ADHD and ways to measure them; and (4) identifying outcomes of importance to health care decision makers, and appropriate ways of measuring them. These four perspectives will now be considered.

3.4.1 Measuring core ADHD symptoms

Measurement of core ADHD symptoms is routine in clinical trials of ADHD and important for comparison purposes and for assessment by decision makers, although it is expected that successful treatment of ADHD will address not only symptomatic improvement but also impairment in social functioning (NICE, 2008).

Table 7 identifies the outcome measures which have been used to measure the effects of conventional medication, psychological interventions, polyunsaturated fatty acids and homeopathy. Information was extracted from the NICE Clinical Practice Guideline (2008); the most recent meta-analysis of PUFAs (Puri & Martins, 2014); and the Cochrane systematic review of homeopathy (Heirs & Dean, 2009).

Table 7. Outcome measures used in interventions for ADHD

Systematic review	Primary Outcome measurement	Secondary Measurements
Heirs & Dean (2009) Homeopathic remedy v placebo remedy	CGI-Parent/Teacher, CPRS-R:L	VLMT, QCB, WISC, CPRS, CGI-T, CPT, ADHD-SC4, MYMOP
NICE (2008) Pooled methylphenidate v placebo (N=12)	Core ADHD symptoms teacher/carer. CPRS, SNAP	?
NICE (2008) Pooled atomoxetine v placebo (N=10)	Core ADHD symptoms (total) teacher/carer. CPRS, SNAP	?
NICE (2009) Pooled psychological interventions v control (TAU, wait	Core ADHD symptoms, CPRS, SNAP. teacher+carer-	Conduct, social skills, emotional

list, no Treatment) (N=10)	rated (end of T'ment/3-6 months post T'ment)	
Puri (2014) Pooled Polyunsaturated fatty acids (N=18)	Conners (various), CBCL ,RBPC,DBD Carer/teacher	Inattention, hyperactivity

__CGI-P__ (Conners Global Index-parent); __CGI-T__ (Conners Global Index-Teacher); __CPRS:-R:L__ (Conners Parent rating scale, revised, long; __CPRS-R:S__ (Conners Parent rating scale, revised, short); __PSQ__ (Conners Parent symptom questionnaire); __CGI-SS__ (clinical global impression-severity scale); __CGI-IS__ (clinical global impression-Improvement scale); __CCT__ Children's checking task; __QCB__ (Questionnaire of Change of Behaviour); __VLMT__(auditory learning test); __WISC__ (Wechsler intelligence test); __CPT__ (continuous performance test); __ADHD-SC4__ (Stimulant Side Effects Checklist); __ACTeRS__ (ADD-H Comprehensive Teacher Rating Scale); __ADHD-RS__ (ADHD rating scale); __CBCL__ (Child Behavior Checklist); __DBD__ (Disruptive Behavior Disorders rating scale); __RBPC__ (Revised Behavior Problem Checklist); __SNAP__ (Swanson, Nolan & Pelham ADHD rating scale. __MYMOP__ (Measure your own medical outcome profile).

Conners Rating Scales.

The most common outcome measurements identified above were Conners Rating Scales in various formats. Most studies used short forms, recommended by Conners for clinical trials (Conners, 2009). Three short measures (all available for completion by carers and teachers) are: the 10 item Conners Global Index (C3GI) (favoured in homeopathy studies); the 18 item DSM ADHD criteria (favoured in trials of fatty acids and medication); and the 12 item Conners' ADHD index (Table 8).

The Conners Handbook states that "although in the past there have been differences in the psychometric properties of the Conners forms that may have led some practitioners to prefer one version over another, the current versions are all about equivalent in terms of strength of norms, reliability and validity" (p14, Conners, 2009).

Table 8. Individual items in three short Conners ADHD measures.

CGI-Total (10)	DSMIV ADHD criteria (18)	ADHD Index (12)
Fidgeting	Fidgets with hands or feet or squirms in seat	Fidgets with hands or feet or squirms in seat
	Leaves his/her seat at school when not supposed to at school	Leaves seat in classroom or other situation where remaining seated is expected
Inattentive, easily distracted	Is distracted when things are going on around him/her	Inattentive, easily distracted
		Distractibility/attention span a problem
	Has trouble keeping attention focussed when playing or working	Gets distracted when given instructions to do something
Fails to finish things he/she starts	Has trouble finishing schoolwork or chores	Does not follow through instructions/fails to complete HW,

		chores, duties
	Has problems organising tasks and activities	Messy or disorganised at home or school
Excitable, impulsive	Gives answers to questions before the questions are completed	Only attends something he's very interested in
Restless or overactive	Is restless or overactive	Avoids/expresses reluctance/has difficulties engaging in tasks that require sustained mental effort
	Is always on the go	
Disturbs other children	Has trouble playing or doing leisure activities quietly	Easily frustrated in efforts
	Interrupts others when they are working or playing	
Cries often and easily	Does not like homework where he/she has to think a lot	Short attention span
Temper outbursts; explosive, unpredictable behaviour	Has trouble listening to what people say to him/her	Has trouble concentrating in class
Mood changes quickly and drastically	Is forgetful in daily activities	
Demands must be met immediately – easily frustrated	Talks too much	
	Loses things necessary for tasks and activities	
	Has trouble waiting in line or taking turns	
	Makes careless mistakes or has trouble paying attention to details	

It was decided to use CGI due to its measurement of emotional aspects, and since the measure has been used in three trials of individualised homeopathic remedies and appears to be sufficiently sensitive. The CGI has a two-factor structure described as restless/impulsive (7 items) and emotional lability (3 items) (Conners, 2009).

The three questions constituting the emotional lability sub-scale score are: 'temper outbursts- explosive, unpredictable behaviour'; 'mood changes quickly and drastically'; and 'cries often and easily'. The remaining seven questions constituting the restless/impulsive sub-score are: 'excitable, impulsive'; 'restless, overactive'; 'inattentive, easily distracted'; 'fidgeting'; 'disturbs other children'; 'demands must be met immediately – easily frustrated'; 'fails to finish things he/she starts') (Conners, 2009).

The measure has convergent validity, correlating with other measures of psychopathology and the Conner's ADHD Rating Scale (Kao & Thomas, 2010), and discriminative validity, accurately distinguishing between the general population and those with ADHD (Conners, 2009).

Swanson, Nolan & Pelham Questionnaire (SNAP-IV)

This questionnaire is similar to Conners 18 item DSM criteria, but much cheaper. It was developed by MTA researchers and the psychometric properties and clinical utility of the SNAP-IV have been demonstrated in multiple studies since its introduction in 2001 (Bussing, et al., 2011). SNAP-IV was added after the study had been running for 6 months, on the advice of the steering committee chairman, who suggested that CGI scores may not be considered adequate indications of specific ADHD improvement.

The SNAP-IV 18 item scale consists of DSMV ADHD items Inattention (items 1-9) and hyperactivity/impulsivity (items 10-18). Symptom severity is rated on a 4 point scale. The average is calculated by totalling the scores and dividing by the number of items for each subset. Scores below 13 (out of 27) are not considered clinically significant; between 13 and 17 considered mild symptoms; 18-22 moderate symptoms; and 23-27 severe symptoms.

3.4.2 Completion of outcome measures

Although pragmatic trials do not generally collect blinded outcomes, the decision was made to collect outcomes from both carers and (probably blinded) teachers. The term 'probably blinded' was used because there is a small chance teachers may ascertain the child's status anecdotally. Measurement of blinded outcomes was considered important due to concern about ascertainment biases, and despite concern that measuring teachers' observations over the long-term may be problematic: teachers change and schools have holidays (Biederman et al., 2004); return of questionnaires is poor (Brazier, et al., 2014); teachers may not observe the kinds of changes expected; busy teachers in large classrooms may not observe subtle changes. Therefore the feasibility of collecting and using blinded teacher outcomes was assessed.

3.4.3 Measures of importance to those directly affected by ADHD

Cunningham (2007) argues that measurement of adaptive function is important and a better predictor of impact on long-term outcomes than ADHD symptoms. It can be measured via the Home situations questionnaire (DuPaul & Barkley, 1992), the Impairment Rating Scale (Fabiano, Pelham, & Waschbusch, 2006), or the Strengths and Difficulties Questionnaire (SDQ) (Goodman, Lamping, & Ploubidis, 2010) which categorizes strengths and difficulties into five scales: emotional problems, conduct problems, hyperactivity, peer problems and

prosocial behaviour. It is one of the most widely used brief questionnaires for assessing child mental health problems.

It was important to measure emotional lability, as an important driver of negative outcomes of those with ADHD (Young, Taylor, & Gudjonsson, 2016). Measurement is possible via a sub-set of the SDQ (5 items) or the CGI (3 items) described above. Another measure is the affective reactivity index (ARI) (Stringaris, et al., 2012) which consists of 7 items: is easily annoyed by others; often loses his/her temper; stays angry for a long time; is angry most of the time; gets angry frequently; loses temper easily; overall, irritability causes him/her problems.

The decision was made to use the emotional lability subscale in the CGI and not add the SDQ, ARI or an adaptive function questionnaire as a further measure, in order to reduce the questionnaire filling burden on participants.

3.4.4 Objective Measures of importance to decision makers

Decision makers are concerned about the use of state funded facilities such as the NHS, social care, criminal justice system, and education. It was decided to ask participants about the number of visits to these institutions, any psychosocial interventions they had taken part in, and about all the medications taken by the child.

Criminality might also be measured by accessing official criminal records obtained from the Ministry of Justice; using the YCAP validated outcome measure; or real-life measurements of numbers of arrests, convictions, aggressive offences, felony charges, incarcerations, re-offence rates. However, it was decided that such detailed questions might be off-putting to carers; and the process of obtaining the permissions required to access criminal records too time consuming at this stage, but may be considered in the future.

ADHD has a high impact in schools, so it was decided to ask teachers to rate levels of classroom disturbance, absenteeism, exclusion and extra resource use such as learning support assistance in the Teacher Questionnaire (Appendix 1b). Like accessing criminality records, accessing education records was considered too time consuming at this stage but may be considered in the future.

3.4.5 Health-Related Quality of Life measurement.

Policy makers such as NICE use preference-based measures to examine the cost-effectiveness of interventions in terms of cost per Quality Adjusted Life Year (QALY). A validated quality of life measure is needed to generate QALYs. Furthermore, Health Related Quality of Life (HRQOL) is increasingly recognised as an important outcome in itself. It is de-

fined as “an individual's subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning”. (Leidy, Rich & Geneste, 1999) and most appropriately assessed from the patient's perspective (Coghill, 2011). The rationale is that assessment of the patient's perspective provides insights into treatment benefits that may be obscured when filtered through the clinician's perspective (Coghill, 2011); and that since what people care about is their wellbeing and ability to play an active role in society, that’s what should be measured (Coulter, 2017).

There are several problems associated with measuring HRQOL in children. These include the influence of age related language development, reading ability and conceptual understanding. Reading ability influences whether children can complete questionnaires (Rebok, et al., 2001). Age has an effect on understanding of concepts: aged between 4 and 6 children can report about concrete domains like pain and medication use, whereas only older children can describe the emotional impact of their illness (Wallander, Schmitt, & Koot, 2001).

Proxy-reported outcome measures for children are discouraged (Food and Drug Administration (FDA), 2009), due to concerns about the concordance between proxy and child ratings (Theunissen, et al., 1998). However, almost all paediatric psychopharmacology trials measuring HRQOL use carer-rated measures. ADHD seriously compromises HRQOL according to carers, with robust negative effects reported consistently which rate the HRQOL of their children as 1.5 - 2 SD below appropriate population norms (Coghill, 2011). Children with ADHD rate their own HRQOL less negatively than their carers and sometimes do not consider themselves as having impaired HRQOL (Coghill, 2011).

Since it is recommended that HRQOL outcomes are included in treatment studies (Coghill, 2011), it was decided to include a HRQOL measure. It is argued that HRQOL outweighs simple short-term symptom reduction as the most important treatment outcome for ADHD; and such outcomes are used to generate cost-effectiveness estimates. It was decided to use proxy ratings: due to the wide age range included in this study; since the other outcomes are completed by carers; and since proxy HRQOL is measured in the majority of ADHD research. Which measure to use is considered next.

HRQOL measures

Examples of HRQOL measures used in studies of medication are: AIM-C (Manos, Frazier, & Landgraf, 2009), CHQ (Child Health Questionnaire) (Landgraf, Abetz, & Ware, 1999), CHIP-CE (Child Health Illness Profile-Child Edition) (Prasad, Harpin, & Poole, 2007), GIPD (Global Impression of Perceived Difficulties) (Wehmeier, Schacht, & Barkley, 2010), PedsQL (Pediatric Quality of Life Inventory) (Varni & Burwinkle, 2006). One ADHD specific measure of HRQOL has been developed (ADHD Impact Module (AIM)) (Landgraf, 2007) but is specifically for adults with ADHD.

Studies investigating the impact of medication treatments on HRQOL in ADHD support a positive short-term effect of medication (largely atomoxetine) that to some extent mirror their effects on ADHD symptoms (Coghill, 2010). No ADHD clinical trials of psycho-social treatments, homeopathy or nutrition measuring HRQOL were found.

It was decided to use the HRQOL measure Child Health Utility (CHU 9D) which was developed in Sheffield (Stevens, 2010), on the advice of Sheffield based researchers who have used it in an ADHD study (Peasgood, et al., 2016). They compared CHU 9D, EQ-5D-Y, (using the adult tariff), and the Weiss satisfaction scale. They recommended CHU 9D but with reservations, since they had a lower response to CHU 9D than EQ-5D-Y. This was driven by question 6 on school and home work: my child has no/a few/ some/ many problems / can't do their homework today, which mostly adolescents failed to answer. The measure was completed by the child, and it was hypothesised that word 'today' was taken literally when it might be a weekend, day off, the child excluded from school or not receiving homework.

The researchers did not recommend EQ5D despite a large effect size driven by issues with self-care/dressing/washing, because although the children reported fairly high levels of problems, it was felt that these were different to those considered when the tariff was derived: children with ADHD have difficulties due to reluctance and difficulty following instructions rather than physical impairment. Their study identified a high level of sleep problems and they recommended inclusion of a question about sleep. One item in CHU 9D asks about sleep and it was decided to analyse this separately: 'last night my child had no/ a few/ some/ many problems sleeping/could not sleep at all'.

CHU 9D

CHU 9D is a paediatric generic preference-based measure of health-related quality of life for children aged 7 to 17, which was developed from qualitative interviews with school age children. It has nine attributes: worried, sad, pain, tired, annoyed, schoolwork/homework, sleep, daily routine and able to join in activities, with five response levels for each.

The preference weights were derived from the application of the standard gamble method from 300 members of the UK adult population (Stevens, 2010). This gave estimates for the importance of change in one item versus change in another item and versus extending years of life, as perceived by adults. The tariff generated a score for each CHU 9D health state on a scale on which 0 is equivalent to being dead and 1 represents full health.

The standard gamble method and valuation by adults (despite the descriptive system being for children) is in line with NICE recommendations (NICE, 2004). This is because it is found that there are challenges eliciting utility values from children (Ungar & Gerber, 2010), and

attempts made to value the CHU 9D with 11–13 year olds found that the standard gamble method did not perform well (Ratcliffe, Couzner, & Flynn, 2011).

The original preference weights were developed to be completed by the children themselves, but adolescent and proxy preference weights for the CHU 9D have since been generated.

3.5 A pilot study, a feasibility study or a full trial?

At the start of this PhD, the plan was to conduct a full trial, building upon the pilot work of the case series already conducted (Fibert, Relton, Heirs, & Bowden, 2016). However, such a plan was considered too ambitious for a PhD, and some feasibility questions remained: could sufficient and suitable therapists be recruited? would the trial design be feasible and acceptable? could recruitment of a representative sample of children with ADHD be accomplished? were the selected outcome measures suitable, deliverable and acceptable?

Therefore, a further pilot study assessing the feasibility of the design and measures was designed. The distinction between a pilot study and a feasibility study is not clear cut. All pilot studies are feasibility studies, but not all feasibility studies are pilot studies (Eldridge, et al., 2016). Feasibility studies ask whether something could be done, should we proceed with it, and if so, how? Pilot studies do the same but are smaller scale studies of future full scale studies. This work fulfils both criteria.

Arain and colleagues (Arain, Campbell, Cooper, & Lancaster, 2010) define feasibility studies as pieces of research done before a main study to estimate important parameters needed to design the main study, such as: the standard deviation of the outcome measure to estimate sample size; the willingness of participants to be randomised and of clinicians to recruit participants; the number of eligible patients; the characteristics of the proposed outcome measure; follow-up rates, response rates to questionnaires, and adherence/compliance rates. Feasibility studies for randomised controlled trials may not themselves be randomised.

A pilot study is considered to be a version of the main study run in miniature to test whether the components of the main study can all work together to ensure recruitment, randomisation, treatment, and follow-up assessments all run smoothly. It may be the first phase of a substantive study to which pilot data can contribute (an internal pilot) or set aside (an external pilot) (Arain, et al, 2010).

3.6 Summary

In this chapter I have discussed shortcomings in current approaches to generating evidence, which are that they are expensive, slow, interventions are not easily comparable, and not answering questions of interest to those wanting to improve long-term negative outcomes. I argue that new approaches to evidence generation are required in order to identify treatments which can improve outcomes for ADHD.

I have justified the choice to conduct a more pragmatic as opposed to a more explanatory trial, and the rationale for a TwiCs approach to pragmatic trial design allowing multiple trials to be embedded within a cohort. Some key design issues were identified and discussed, such as recruitment of a representative sample, measurement of outcomes of importance to stakeholders, and the requirements of NICE, as the national adviser regarding NHS treatments. Potential outcome measures were identified and the rationale for the selected outcomes was described.

Having identified and described the TwiCs trial design, in the next two chapters I will describe the two interventions selected: their evidence base and any particular considerations.

Chapter 4 Homeopathy

This chapter describes one of the interventions selected to be tested using the TwiCs design. It explains exactly why the trial intervention is described as 'treatment by a homeopath', rather than 'homeopathy' or 'homeopathic remedies'. It describes the therapeutic system: the fundamental principles upon which homeopathy is based, the principles by which remedies are made and the principles by which a prescription is made. The different ways that homeopathic treatment is accessed and implemented is outlined. The safety of homeopathy is assessed. A literature review of homeopathy for ADHD is conducted, and the evidence base for the different aspects of homeopathy tested is critiqued in terms of their internal, ecological and model validity. Poor ecological validity is postulated as an explanation for research findings. Finally, the comparative consecutive case series preceding this study is briefly described, with regard to the preliminary feasibility it provides.

4.1 Definition and description

Homeopathy (greek: homoios meaning same or similar, pathos meaning suffering) is "a system of therapeutics founded by Samuel Hahnemann (1755-1843) based on the Law of Similars whereby 'like cures like' (Fisher, 2012). Diseases are treated by highly diluted substances that cause, in healthy persons, symptoms like those of the disease to be treated" (https://meshb.nlm.nih.gov/#/record/ui?ui=D006705 accessed 13/1/17). It is postulated that "nano-amounts effect significant change over long periods" (Barnes & Winterson, 2007).

The therapeutic system consists of several interacting components: homeopathic medicines known as remedies, the homeopathic consultation, and the principles of homeopathy (Relton, O'Cathain, & Thomas, 2008). Homeopathic remedies are made from material substances from multiple sources (e.g. extracts from plants, animals, minerals or chemicals). Nano-doses of these substances are made up by a process known as potentisation which involves repeated dilutions, with sucussion (vigorous shaking) between each dilution (Fisher, 2012). The dilution ratio is one part medicinal substance to 99 parts water, with a specific number of sucussions between each dilution. Centesimal (C), millesimal (M) and 50 millesimal (LM) scales are used. The standard interval range for remedies is : 6C, 9C, 12C, 15C, 30C, 200C, 1M, 10M, 50M, LM. In many cases medicines are diluted to such an extent that no molecules of the original substance can be identified.

Homeopathic treatment involves an in-depth consultation with a practitioner, where information about the patient's physical, general, mental and emotional symptoms are gathered. The patient's presenting symptoms are then matched with an appropriate homeopathic remedy. There is some similarity between consultations carried out by homeopaths and psychological interventions, such as the amount of time given to patients, practitioners' empathy, and patients' disclosure of problems. However, homeopathic treatment differs from psychological interventions in a number of ways, particularly with regards to the homeopath's focus on the patients' symptoms and complaints and the prescription of a homeopathic remedy.

The principle of potentisation is colloquially known as the principle of the 'minimum dose', whereby the more the remedy is potentised and succussed, the more effective or potent it becomes. Its implausibility has given rise to much scientific controversy about homeopathic treatment. Hahnemann initially used doses similar to those used in contemporary conventional medicine, but gradually reduced the size of his doses after empirical observation, to 'ultramolecular dilutions' (Fisher, 2012).

The principle of similitude is colloquially known as 'like cures like' or 'similia similibus curentur'. This principle considers that a substance which can produce a spectrum of symptoms in a healthy person may cure the same spectrum of symptoms in a sick person. If symptoms are correctly matched, then the person is stimulated to heal themselves. The principle is similar to that of hormesis: the stimulatory or beneficial effects of small doses of toxins (Fisher, 2012), and has been known of since ancient times: "by similar (homoia) means a disease arises and by administering similar things health is restored from sickness" (Hippocrates). It has correspondences in conventional medicine, for example immunisation, and methylphenidate, which is a stimulant used to treat an over-stimulated nervous system.

The principle of individualisation is colloquially known as 'the patient not the cure' (Blackie, 1978). The matching of substance to symptom is patient rather than condition specific. Patients with the same diagnosis are likely to receive different remedies. For example allium cepa (onion) may be prescribed to treat a presentation of weepy hay fever, or natrum muriaticum (salt) prescribed for a presentation of hayfever with violent, frequent sneezing. The in-depth consultation between a homeopath and a patient ascertains the symptoms to be matched to enable the individually tailored prescription.

4.1.1 Use and provision of homeopathy

In the UK, treatment by a homeopath is practiced both by medically qualified homeopathic practitioners and by professional homeopaths. Treatment by a homeopath is available in some NHS hospitals, from some NHS GPs who have undertaken extra training, and privately.

Individually tailored remedies are obtained from homeopaths, and homeopathic remedies can also be bought over the counter or ordered from homeopathic pharmacies. These generic remedies are selected according to possible clinical indications, and typically constitute a 'catch all' approach (e.g. a hay fever complex contains a basket of remedies useful in common manifestations of hay fever). They are widely used; more easily trialled being 'per protocol' treatments; and cheaper, since the main cost of homeopathic treatment is incurred in the consultation. However, they are easy to select inappropriately when the remedy(ies) do not cover the patient's specific symptoms. Taking inappropriately matching remedies generally means there is no reaction. For this reason the effectiveness of Over-The-Counter (OTC) purchased remedies is likely to be reduced compared to the effectiveness of individually tailored remedies since prescription is generic rather than specific.

4.1.2 The safety of homeopathy

Seven reviews of the evidence of the safety of homeopathy indicate that homeopathic remedies may cause mild to moderate transient side-effects, but not strong or persisting side-effects (Bornhöft, et al., 2006; Dantas & Rampes, 2000; European Central Council of Homeopaths, 2009; Grabia & Ernst, 2003; Woodward, 2005). No interactions with conventional drugs have been reported. A potential reported risk involves delay in referral for necessary conventional examination and/or treatment (Posadzki, Alotaibi, & Ernst, 2012). However, evidence indicates that such cases are rare (European Central Council of Homeopaths, 2009). Only one study to date has systematically documented the occurrence of adverse events during homeopathic treatment for ADHD (Jacobs, Williams, Girard, Njike, & Katz, 2005), and found none in either group.

4.1.3 Different methods used by homeopaths

Over time, a variety of methods to arrive at individually tailored prescriptions have been developed, and generally homeopaths apply a pluralistic approach. Some different, unusual methodologies have been trialled for ADHD: Sensation methodology (Jacobs, et al., 2005) was not found to be effective; and Boenningausen methodology (Frei, et al., 2005), which was trialled during a pilot phase exploring methodologies to achieve optimal clinical effectiveness (Frei, Thurneysen, von Ammon, & Jacobs, 2006) and was found to be effective. There is considerable scope to explore different methods and understand which ones may lead to more effective outcomes.

4.1.4 Treatment by a homeopath

Homeopathy, as practiced in clinics, may be considered to include the following three interacting components qualifying it to be considered a complex intervention (Relton, O'Cathain, & Thomas, 2008):

1. the homeopathic remedy
2. the therapeutic consultation
3. the application of the principles of homeopathy

The three components are inextricably linked, in that the therapeutic consultation is necessary for identification of the correct homeopathic remedy, which is applied according to the principles of homeopathy. The extent to which interacting components are included in trials is considered when the treatment's ecological validity is assessed (4.2.6, Table 12).

4.1.5 The testing of the therapeutic system of homeopathy

Homeopathy research is still in its infancy, and there is considerable scope to explore optimum research designs. Most RCTs of homeopathy to date test generic homeopathic remedies, that is without consultations or application of homeopathic principles. Up to 2013 there were a total of 137 placebo-controlled RCTs published in peer reviewed journals of which 96 were of generic remedies. This means the significant majority of homeopathy trials have very poor ecological validity.

41 trials have tested the efficacy of individually tailored homeopathic remedies, whereby the active arm typically received components 1,2 and 3, and the placebo arm received components 2 and 3. These trials have better ecological validity. There are just 12 RCTs with good ecological validity, whereby components 1, 2 and 3 are present in the verum arm but not in the comparison arm (Mathie, Hacke, Clausen, Nicolai, & Riley, 2013).

Regardless of positive or negative outcomes, systematic reviews and meta-analyses of the trials of homeopathy all conclude that the homeopathy used in trials is unlikely to reflect usual practice (Kleijnen, Knipschild, & Ter Riet, 1991; Linde, et al., 1997; Cucherat, Haugh, Gooch, & Boissel, 2000; Ernst, 2002; Dean, 2004).

The absence of all components of the therapeutic system in trials is an explanation for why such trials can fail to demonstrate efficacy and may be contributing to the heated debate which surrounds the therapy. Furthermore, homeopathic treatment is regarded as a process, therefore blinding the practitioner, or limiting remedy testing to single remedies contributes to reduced ecological validity (Relton, 2013).

Observational surveys may better capture the broad effects of homeopathic treatment: the Bristol Homeopathic Hospital analysed 23,000 outpatient consultations from 1997 to 2003 (Spence, Thompson, & Barron, 2005) and found > 50% self-rated health improvements and >70% clinical improvements. 66% of children rated their health as 'better' or 'much better' and 80% stated a degree of improvement. Similar improvement ratings were seen in Tun-

bridge Wells homeopathic hospital in 74% of 1372 patients (Clover, 2000); and in Liverpool in 76.6% of 1100 patients (Richardson, 2001).

Surveys may succeed in capturing improvements under homeopathic treatment, and have large sample sizes, but evidence is low quality due to use of patient reported, unvalidated outcomes and lack of randomisation. Of even lower quality are the descriptive case studies which are the principle means by which homeopaths communicate the effectiveness of their treatment (e.g Fibert, 2015b)

A study of relevance to this thesis was conducted in conjunction with local authorities (McLean & Garland, 2005). Treatment by a homeopath was provided to 10 children selected by 10 schools as being in danger of exclusion. The study used a simple, objective measure (school exclusion), and no children were excluded. However, again there was no comparator and the study has not been published in a peer reviewed journal.

It is postulated that homeopathic treatment might be broadly helpful for children with ADHD, who tend to present heterogeneously and with co-occurring diagnoses, because the therapy takes a holistic approach, and treatment responses are expected to be global and non-specific. Furthermore, the ability to treat co-occurrent diagnoses within one therapeutic modality is considered by homeopaths to be a strength of their approach. One study of 43 multimorbid patients (with at least 3 co-occurrences) has been conducted, which found those treated homeopathically experienced 47% improvement after one month and 63% after two months, rating each symptom's intensity on a scale of 0-10 (Frei, 2015).

Measurement of specific improvements in specific conditions may not capture the global health improvements expected to occur during homeopathic treatment. For example in one case (Fibert, 2015a) from my case series (Fibert, Relton, Heirs, & Bowden, 2016) a child presented with diagnoses of ADHD, autism, ODD, dyslexia, hypertonia, recurrent ear infections, sleep apnoea, eczema, asthma, allergies (dairy products, nuts, bees and wasps), constipation, tics, chronic pneumonia, and collapse of left lung. Only improvements in ADHD were measured despite improvements in the other conditions.

4.1.6 The cost effectiveness of homeopathic treatment

Cost-effectiveness studies of homeopathic treatment for a variety of conditions suggest that integration of homeopathy is associated with better outcomes for equivalent costs. (eg (Trichard, Chaufferin, Dubreuil, Nicoloyannis, & Duru, 2004; Witt, et al., 2005).

Informal cost-effectiveness indications for ADHD suggest reduced costs compared to conventional treatment. The therapy is relatively cheap to implement: the majority of the cost is the consultation and homeopathic remedies are included in that cost. Annual costs for my

case series (2010-12) were approximately £300 per child comprising consultation costs @ £55 for a first consultation and £35 for follow ups (Fibert, 2016).

An evaluation of homeopathic treatment compared to stimulant treatment in Switzerland for ADHD found homeopathy costs to be 75% of stimulant costs in the first year, and 50% in following years. Over a ten year period homeopathic treatment per single child cost CHF 2120 ($ 1705) compared to CHF 3650 ($2920) with stimulant therapy (von Ammon, 2012). Cost benefit analysis of children in danger of exclusion (McLean & Garland, 2005) found homeopathy to be associated with less than half the costs (£6713) compared with mainstream behaviour support (£15120).

4.2 A literature review of homeopathy for ADHD

This section reviews the evidence base for homeopathy and ADHD. Since considerable heterogeneity exists between studies, meta-analysis was not conducted.

4.2.1 Search methods for the literature review

Inclusion criteria were: all published primary studies of efficacy and effectiveness, randomised, quasi randomised, not randomised, cohort studies and case studies greater than n=1. Studies had to include at least one aspect of homeopathy (the homeopathic remedy, the homeopathic consultation, or the application of the principles of homeopathy). They could use any method and prescribe any number of homeopathic remedies. Trials could be of any duration, and participants any age, including adults.

Studies could measure ADHD as a primary or a secondary measure. They could use any comparator, (eg placebo, treatment as usual, baseline or another intervention) and any outcome measure: validated or non-validated; self, carer, clinician or teacher-rated; specific measure of ADHD or generalised improvement rating, measure of wellbeing, or quality of life; measurement of accompanying symptoms such as anxiety, anger, opposition, or school performance.

Exclusion criteria were editorials and commentaries; studies where the intervention did not conform to any homeopathic principles; and studies with no outcome measurement.

Search strategy

Databases were searched from 1960 to 2016 using the terms: “homeopathy” AND “ADHD" OR "attention deficit" OR "hyper kinetic" OR "HKD", inception – 2016. The following data bases were searched: MEDLINE, AMED, BIOSIS, BMC CAM: BMC Complementary and Alter-

native Medicine, CAMbase, CINAHL, CENTRAL, ECH, ERIC, Embase, Hominform, IDHDR, PsycINFO, RCCM.

In addition, hand searching of the following was conducted: English language homeopathy journals; experts publishing studies in the field (Professor Frei, Professor von Ammon, Dr Jacobs); university websites where homeopathy research for ADHD was known to have been conducted (Bern, Washington and Johannesburg); homeopathy and complementary therapy conference proceedings (the International Conference for Complementary Medicine Research; the Homeopathy Research Institute; and the Children's Complementary Therapies Network).

Quality assessment of studies

Studies were assessed for their internal validity using the Cochrane collaboration's tool for assessing risk of bias (Higgins, 2011)[1]. They were assessed for their ecological validity according to the extent to which three identified components of homeopathy were present (Relton, O'Cathain, & Thomas, 2008)[2] (section 4.1.4). They were assessed for their model validity (the degree to which design and setting corresponds to best practice), using recommendations set out by Mathie (2013)[3]

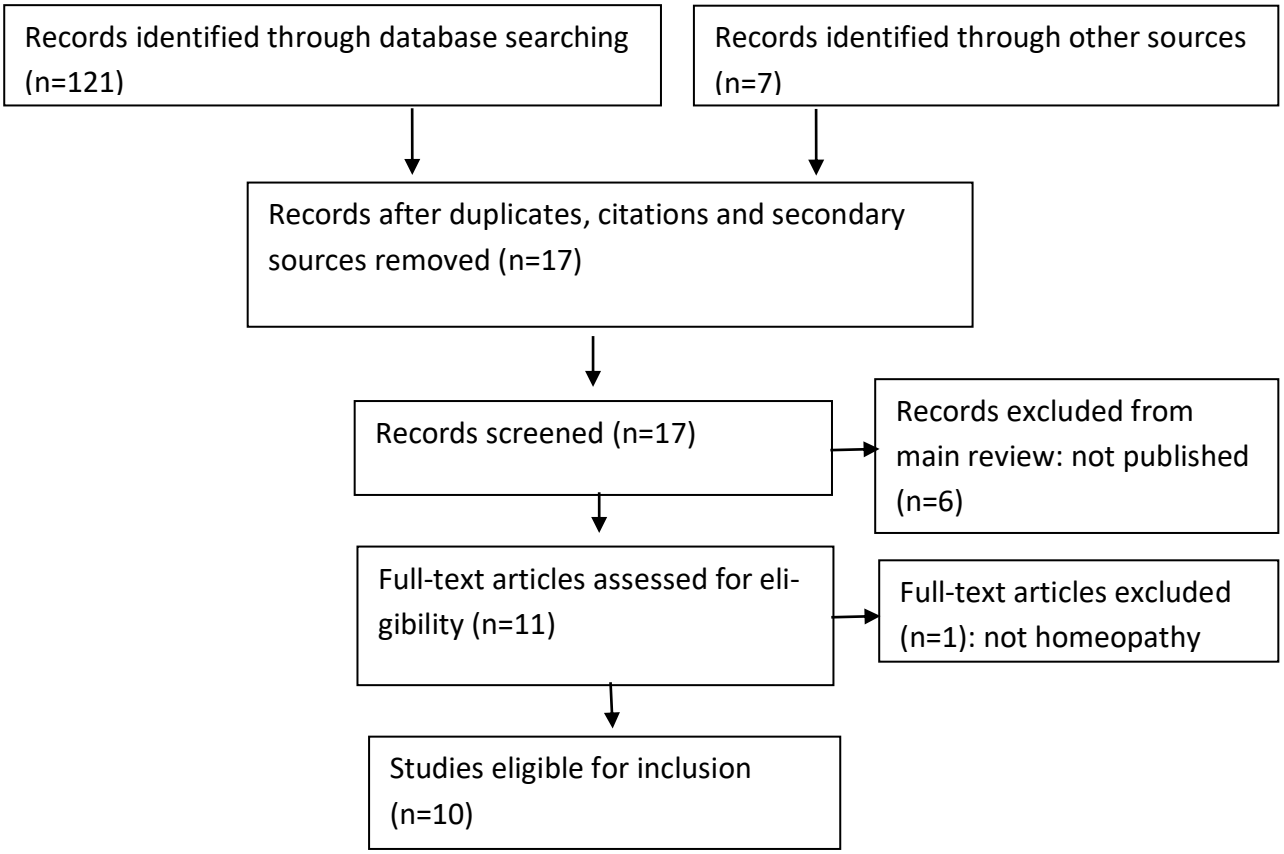
[1] Domain I: selection bias, random sequence generation. Domain II: selection bias, concealment of allocation sequence Domain III: performance bias, blinding of participants and researchers Domain IV: detection bias, blinding of outcome assessment Domain V: attrition bias, incomplete outcome data. Domain VI: reporting bias, selective reporting of outcomes Judgement is made as to whether risk of bias is high, low or unclear.

[2] Domain I: The homeopathic medicine. Domain II: The therapeutic consultation. Domain III: The application of the principles of homeopathy

[3] Domain I: A significant body of accredited homeopaths would support the rational for the intervention. Domain II: The homeopathy used in the trial is based on homeopathic principles plus available literature sources. Domain III: The practitioner is a suitably qualified and experienced homeopath. Domain IV: The outcome measure reflects the main effects expected of the intervention. Domain V: The outcome measure is capable of detecting change. Domain VI: The length of follow-up for the main outcome measure is appropriate to detect the intended effect of the intervention

4.2.2 Results of the literature search

A Prisma flow chart outlines the results of search strategy at each stage.



4.2.3 Description of studies

See Appendix 11. Ten studies were identified as eligible for inclusion, summarised in Table 9. Three categories of study were identified: RCTs of standardised homeopathic products; RCTs of generic homeopathic products; and non-randomised case series.

Category 1 (generic homeopathic products): (Razlog, Pellow, & White, 2012 & Strauss, 2000).

Category 2 (studies of individually tailored homeopathic remedies): four RCTs (Lamont, 1997; Frei, et al., 2005; Jacobs, Williams, Girard, Njike, & Katz, 2005; Oberai, Varanasi, Mishra, Singh, & Nayak, 2013).

Category 3 (case series): four case series (Fibert, Relton, Heirs, & Bowden, 2016; Barvalia, Oza, Patil, Agarwal, & Mehta, 2014; Brulé, et al., 2014; Frei & Thurneysen, 2001).

Table 9. Summary of the homeopathy studies for ADHD

Category	*Study and venue*	*What is tested*	*Research design*	*Comparator*	*Measurement*	*Duration of study*	*Statistical results*
1	Strauss, 2000. *S.A*	Generic compound product	DB-pc-RCT	Placebo pill	CPRS	2 months	SMD -0.17 (CI -1.05, 0.71)
1	Razlog, 2012. *S.A*	Non-Individualised homeopathic remedy	DB-pc-RCT	Placebo pill	CPRS	3 weeks	Pre/post test mean 15.89, 13.89
2	Lamont, 1997. U.S.A	Individually tailored homeopathic remedies	SB-pc-RCT	Placebo pill	Unvalidated likert scale	40 days	SMD -0.65 (CI -1.27, -0.03)
2	Frei 2005. *Switzerland*	Individually tailored homeopathic remedies	DB-pc-RCT	Placebo pill	CGI-P	5 months	SMD -1.67 (CI -3.32, -0.02)
2	Jacobs, 2005. *U.S.A*	Individually tailored homeopathic remedies	DB-pc-RCT	Placebo pill	CPRS	18 wks	SMD 0.17 (CI -0.43, 0.77)
2	Oberai, 2013. *India*	Individually tailored homeopathic remedies	DB-pc-RCT	Placebo pill	CPRS	1 year	SMD= .51 (GLM) 0.48 p= .0001
3	Frei 2001. *Switzerland*	Homeopathic treatment	Case series	baseline	CPRS	3.5 months	Pre/post test mean 20.6, 9.27
3	Barvalia, 2011. India	Homeopathic treatment	Self-controlled pre-post intervention	6 months usual care	AHS	1 ½ years	F 210.599 (p = .0001
3	Brule, 2014. *Canada*	Homeopathic treatment	Case series	baseline	CPRS	1 year	Pre/post-test median 85.5, 74.0
3	Fibert, 2016. *U.K*	Homeopathic treatment	Controlled case series	Similar time and attention	CPRS	1 year	F 9.06, p=.005

SB = single blinded; DB = double-blinded. Pc = placebo-controlled. Rating Scale. AHS: Autism Hyperactivity Score. CPRS: Conners Parent Rating Scale. CGI-P: Conners Global Index-Parent. SMD = standardised mean difference

The studies were methodologically heterogeneous: whilst half used conventional homeopathic methodologies, half used unusual methodologies or tested unusual standardised products, unlikely to be used in real-life clinical practice (Table 10).

Table 10. The heterogeneity of homeopathic methodologies and products used in homeopathy ADHD studies.

Standardised homeopathic products		**Individualised homeopathic remedies**	
Generic remedy	**Generic compound remedy**	**Conventional**	**Unconventional** (*not taught or commonly used in the UK*)
Razlog, 2012 (valeriana officinalis)	Strauss, 2000 (selenium homaccord)	Lamont, 1997	Frei, 2001 and 2005 (Boenninghausen methodology)
		Brule, 2014	Jacobs, 2005 (Sensation methodology)
		Oberai, 2013	
		Fibert, 2016	
		Barvalia, 2011	

4.2.4 Population characteristics of included studies

A total of 515 participants (minimum study population 20, maximum 115) took part: 50 in RCTs of standardised homeopathic remedies; 290 in RCTs of individualised homeopathic remedies; and 175 in case series. Children were aged 5 - 16. Studies were conducted in South Africa, the USA, Switzerland, UK, India and Canada (Table 9).

4.2.5 Design Characteristics

RCTs of homeopathic remedies were placebo-controlled, which meant an identical looking placebo pill of the standard or individually tailored remedy. One case series compared homeopathic treatment with similar time and attention (Fibert, Relton, Heirs, & Bowden, 2016); two case series compared homeopathic treatment with baseline (Frei & Thurneysen, 2001 & Brulé, et al., 2014); and one within subjects study compared 6 months observation with 1 year of homeopathic treatment (Barvalia, Oza, Patil, Agarwal, & Mehta, 2014).

All RCTs were blinded. Three were double-blinded: either practitioner and participants (assessors) were blinded (Frei, et al., 2005 & Jacobs, Williams, Girard, Njike, & Katz, 2005); or participants and teachers (assessors) were blinded (Oberai, Varanasi, Mishra, Singh, & Nayak, 2013). Three RCTs were single blinded whereby participants (assessors) were blinded (Lamont, 1997; Razlog, Pellow, & White, 2012; Strauss, 2000). No blinding occurred in the Case Series.

Length of study varied between 21 and 547 days (Table 9). All studies except two used Conner's questionnaires as their primary outcome measurement (Conners, 2009). The other measures used were an unvalidated rating scale ranging from -2 to +2 (Lamont, 1997), and the autism hyperactivity scale (reduction in hyperactivity, impulsivity, tantrums & self-injurious behaviour) (Barvalia, Oza, Patil, Agarwal, & Mehta, 2014).

One study used a double crossover design (Frei, et al., 2005) based on pilot findings (Frei & Thurneysen, 2001) that homeopathic effects were undetectable one month after stopping the homeopathic remedy. For this unusual design all participants' individually tailored homeopathic remedies were found pre-trial based on 50% remission of symptoms. Then participants were randomised and took either a homeopathic remedy or placebo remedy for 6 weeks to achieve the crossover design. One study had a single crossover design (Lamont, 1997) whereby placebo participants subsequently received homeopathic remedies. The other RCTs and one case series had parallel arms but no crossover.

Some studies documented the number of 'tries' it took to find a homeopathic remedy which participants responded to. Frei (2006) found it took a median of 3 tries (range 1-9); Brule (2014) found it took an average 1.68 (range 1-5); and Oberai (2013) found it took only one. Results may reflect practitioner expertise.

4.2.6 Methodological quality

Internal Validity

Risk of Bias is assessed as high, low, or unclear (Higgins, Gøtzsche, & Jüni, 2011) (Table 11).

Most RCTs published adequate descriptions of random sequence procedures, allocation concealment procedures, attrition, outcome assessment, data, and were double-blinded. One study randomised by alternation (Lamont, 1997). This study was also at risk of bias due to single blinding and use of an unvalidated outcome measurement.

The two RCTs of generic remedies were deemed at high, confirmed risk of selective reporting since positive results in the narrative description did not tally with statistical results. Only intervention change scores were described and discussed with no statistical comparison of the placebo arm despite it being a component of the trial design. Examination of the data found no significant difference between placebo and change scores (both improved) (Razlog, Pellow, & White, 2012; Strauss, 2000).

Case series and the within-subject study were at risk of bias due to lack of randomisation or blinding.

Table 11. Risk of bias of homeopathy studies for ADHD

	Strauss, 2000	*Razlog, 2012*	*Lamont, 1997*	*Frei 2005*	*Jacobs, 2005*	*Oberai, 2013*	*Frei 2001*	*Barvalia, 2011*	*Brule, 2012*	*Fibert, 2016*
Selection bias: random sequence generation	low	Low	Unclear (alternate assignment)	low	low	low	high	high	high	Unclear (consecutive assignment)
Selection bias: allocation concealment	low	Low	Unclear (PI knew allocation)	low	low	Unclear (PI knew allocation)	high	high	high	high
Performance bias: blinding of participants & researchers	low	Low	Unclear. Participants but not researchers blinded	low	low	Unclear. Participants but not researchers blinded	high	high	high	high
Detection bias: blinding of outcome assessment	unclear	Unclear	high	low	low	low	high	high	high	high
Attrition bias: incomplete outcome data	high	High	low	low	low	low	low	low	low	low
Reporting bias: selective reporting	high	High	low	low	low	low	low	low	low	low

Judgement is made as to whether risk of bias is high, low or unclear ((Higgins, Gøtzsche, & Jüni, 2011).

Table 12. Ecological validity of homeopathy studies for ADHD

	Strauss,2000	*Razlog, 2012*	*Lamont, 1997*	*Frei, 2005*	*Jacobs, 2005*	*Oberai, 2013*	*Frei 2001*	*Barvalia, 2011*	*Brule, 2014*	*Fibert, 2016*
The homeopathic remedy	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The therapeutic consultation.	No	No	Unclear: one consult	No	Yes	Yes	Yes	Yes	Yes	Yes
The application of the principles of homeopathy	No: no individualisation, no similimum	No: no individualisation, no similimum	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Judgement is made as to whether each element is included: yes, no or unclear (Relton, O'Cathain, & Thomas, 2008)

Table 13. Model validity of homeopathy studies for ADHD

Study name	*Strauss, 2000*	*Razlog, 2012*	*Lamont, 1997*	*Frei 2005*	*Jacobs, 2005*	*Oberai, 2013*	*Frei 2001*	*Barvalia, 2011*	*Brule, 2014*	*Fibert, 2016*
Homeopaths would support the rationale	No	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Intervention consistent with homeopathic principles	No	No	Yes	Unclear: no consultation	Unclear: infrequent prescribing	Yes	Yes	Yes	Yes	Yes
Suitably qualified and experienced homeopath.	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Main outcome measure reflects key effects	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measure capable of detecting change	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Length of follow-up appropriate	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes

Ecological Validity.

Homeopathic aspects considered were consultation, remedies, and principles (Relton, O'Cathain, & Thomas, 2008).

All participants received one pre-trial consultation in two RCTs (Frei, et al., 2005 & Lamont, 1997). All participants received two consultations during the treatment period in two RCTs (Oberai, et al., 2013 & Jacobs, et al., 2005). Treatment groups received consultations every 6-8 weeks in Case Series; there were no consultations in RCTs of generic products.

The potencies and frequency of administration of the homeopathic remedies varied. Two studies gave low potencies twice daily (Strauss, 2000 & Razlog, Pellow, & White, 2012). Four studies gave LM potencies administered daily (Frei & Thurneysen, 2001; Frei, et al., 2005; Oberai, et al., 2013; Brulé, et al., 2014). Lamont (1997) used 200C potencies administered daily. Jacobs et al.(2005) used a single dose of a 1M potency. Potency and frequency of dosage was varied in two studies (Fibert, et al., 2016 & Barvalia, et al., 2014).

The two RCTs of generic homeopathic remedies have very poor ecological validity. Arguably they should not be included in systematic reviews assessing the effectiveness of homeopathic treatment for ADHD (e.g. Heirs & Dean, 2009). Results from these studies pertain to the suitability of the generic remedies tested, not the effectiveness of the therapeutic system.

The lack of homeopathic consultations in some RCTs influences their ecological validity since neither the process of treatment nor appropriate selection and assessment of remedies is allowed. The best ecological validity occurs in case series.

Model validity

Model validity was adequate across most domains apart from consistency to homeopathic principles (covered in the previous section). Table 14 summarises the Internal, Ecological and Model Validity of studies. This was done numerically: high scores represent poor internal, external or model validity, and low scores represent good internal, external or model validity. Failure to represent each domain scored 2; unclear or partial representation scored 1; achievement of the domain scored 0.

Table 14. Summary of the Internal, ecological and model validity of studies

Category	*Study and venue*	*Internal Validity*	*Ecological validity*	*Model Validity*	*TOTAL SCORE*
1	Strauss, 2000	5	6	7	18
1	Razlog, et al., 2012	5	6	7	18
2	Lamont, 1997	5	1	4	10
2	Jacobs, et al., 2005	0	0	3	3
2	Frei, et al., 2005	0	4	4	8
2	Oberai, et al., 2013	3	0	0	3
3	Frei, et al., 2001	8	0	0	8
3	Barvalia, et al., 2011	8	0	0	8
3	Brule, et al., 2014	8	0	0	8
3	Fibert, et al., 2016	7	0	0	7

Low scores indicate better validity

4.2.7 Discussion of the identified studies

Two RCTs had a good balance of ecological, model and internal validity according to their low total scores in Table 14. In both cases, homeopathic treatment occurred according to usual practice meaning they had good ecological validity. One of these RCTs had reduced model validity because only one dose of the homeopathic remedies was given (Jacobs, et al., 2005). The other had reduced internal validity (Oberai, et al., 2011) because the assessor was not blinded.

Studies were generally heterogeneous, with moderators such as consultation, homeopathic methodology, homeopathic consultation, frequency of dosage, application of homeopathic principles, and study design, all potential confounders.

RCTs of standard homeopathic products

The two RCTs of standardised homeopathic products have poor internal, ecological and model validity and show no evidence of being efficacious. Both came from MSc studies conducted by trialists inexperienced in either homeopathy or trial methodology.

RCTs of personally tailored homeopathic remedies

The RCTS of individually tailored homeopathic remedies largely achieved a satisfactory balance of internal, ecological and model validity, although Jacobs used an unusual homeopathic methodology, and doses of homeopathic remedies were infrequent, as recommended for this methodology. It is argued that this explained the lack of statistically significant differences found in this study (Frei, Thurneysen, von Ammon, & Jacobs, 2006) since other

studies found that homeopathic remedies require taking frequently. Frei based his crossover trial design around pilot finding that effects could not be detected one month after remedies were stopped; Lamont found half his participants had relapsed 2 months after trial end; and Razlog reported scores worsening the week after treatment stopped.

Frei's RCT has good internal validity, but model validity is unclear due to the cross-over aspect of the trial design, because homeopaths would assume some carry over effects. This study did not allow any change in the homeopathic remedy, which is unlike usual practice.

Oberai's study found highly significant statistical differences compared to the other studies. This may reflect the expertise of the practitioners (homeopathy is common in India); high fidelity (despite using Intention to Treat methodology, little attrition occurred); or biased reporting/recording. The study was only single blinded, and the Principal Investigator knew the sequence allocation, which reduced its internal validity.

The use of an unvalidated outcome measurement, quasi-randomisation and single blinding by Lamont (1997) requires these results to be treated with caution.

Case series

All the unblinded Case Series are inevitably at risk of bias. They are, however, representative of homeopathic treatment as experienced in clinical practice, and can provide an estimate of carer-rated effects of treatment by a homeopath for their child.

4.2.8 Statistical Results of the identified studies

Meta-analysis was not conducted due to the heterogeneity of identified studies. Table 9 itemises the statistical results. In summary:

- Two RCTs of standardised homeopathic remedies prescribed daily found no difference between placebo and verum remedies as reported by carers blind to treatment status (Razlog, Pellow, & White, 2012 & Strauss, 2000)
- An RCT of individualised homeopathic remedies prescribed infrequently according to unusual methods found no statistically significant difference between verum and placebo remedies according to blinded carers and teachers (Jacobs, et al., 2005)
- Three RCTs of individualised homeopathic remedies prescribed daily found a statistically significant benefit according to blinded carers (Frei, et al., 2005 & Lamont, 1997) and blinded carers and teachers (Oberai, et al., 2013) however, one study used a non-validated measure (Lamont, 1997)

- One within-subject study in children with autism found a significant effect on their hyperactivity symptoms according to an independent clinical psychologist (Barvalia, et al., 2014)
- Three case series' found statistically significant differences between homeopathic treatment and similar time and attention (Fibert, Relton, Heirs, & Bowden, 2016) or baseline (Brulé, et al., 2014 & Frei & Thurneysen, 2001) according to unblinded carers

4.2.9 Level of evidence generated by the identified studies

In order to determine what level of evidence currently exists, the Oxford University Levels of Evidence were used (Table 15).

Table 15. Levels of Evidence

Level I	the existence of meta-analyses and/or systematic positive reviews
Level IIa	controlled multiplied experiments, randomised, positive results
Level IIb	some controlled experiments, randomised, positive results
Level IIIa	study with multiple cohorts, positive results
Level IIIb	study with some cohorts, positive results
Level IV	opinion of experts (clinical and daily cases)

Taken from (Howick, et al., 2011)

According to these criteria, and depending on how many constitutes 'some', there is level IIb evidence that individualised homeopathic remedies are efficacious. There is level IIIb evidence for case series documenting the effectiveness of treatment by homeopaths as experienced in clinical practice. There is no evidence that the standardised homeopathic remedies tested are efficacious for ADHD.

Implications for potential trial designs

The RCTs represented here supposedly tested the *efficacy* of homeopathic remedies, that is, performing under ideal conditions, in comparison with placebo remedies. However, they do not perform under ideal conditions, since remedies are not prescribed optimally, that is, according to homeopathic principles. Furthermore, usual treatment protocols are not observed (regular consultations, freedom to vary remedy, potency and/or dosage according to individual need). The measured effects of homeopathic remedies are therefore likely to be underestimates.

Studies are not informing us about the effectiveness of homeopathic treatment as experienced in clinical practice. They are not trials of *effectiveness* as recommended by the MRC for complex interventions (Medical Research Council, 2000), the Cochrane systematic re-

view of homeopathy for ADHD (Heirs & Dean, 2009) and for CAM research in general (Witt, et al., 2012). Nevertheless, such studies are used to decide whether treatment by homeopaths for children with ADHD is effective.

Another issue is that studies tend to use only one homeopathic physician, one homeopathic method, or one particular homeopathic remedy. They therefore relate to the effectiveness of that particular method/practitioner or remedy. To test whether use of the therapeutic system of homeopathy might improve outcomes requires testing its real-world effectiveness. This means using a variety of practitioners, prescribing according to a variety of methods, and freedom to manage prescriptions.

Those studies which best represent the therapeutic system (meaning that they have good ecological validity) are Case Series. However, they are at increased risk of bias due to lack of randomisation, comparator or blinded outcome measurement. An important consideration is how to reduce the risk of bias and retain the integrity of the therapeutic system.

4.3 Preliminary feasibility: a comparative consecutive case series

4.3.1 Description of study (Fibert, Relton, Heirs, & Bowden, 2016)

20 Children with a diagnosis of ADHD were consecutively recruited from a variety of venues to receive homeopathic consultations every 6 weeks and take homeopathic remedies between consultations, for one year. To fulfil the requirements for an MSc dissertation, 10 children were subsequently recruited for comparison, and received similar length visits from the same homeopath for 4 months consisting of a supportive chat, but not homeopathic case taking or homeopathic remedies.

Carers completed Conner's Parent Rating Scale, revised long version (CPRS-R: L) every 3 months (Conners, 2009) and the patient generated 'Measure your Own Medical Outcome Profile' (MYMOP) (Paterson & Britten, 2000) at the end of each consultation.

Three families did not fit eligibility criteria and new families were recruited, and three families did not complete one year of treatment due to relationship breakup (N=2) and ill health of a sibling (N=1).

Improvements were observed from baseline to 1 year: t (17) = 6.94, p=.000) with the greatest change from baseline to four months (mean change 8.80, p = .001.) A two way mixed ANOVA comparing treatment group with control group found a significant interaction between group and treatment over time (Wilks Lambda = .721 F (1, 28) = 10.85, p= .003).

4.3.2 The feasibility of the methods used to conduct the comparative case series

This study explored the feasibility of: the outcome measures; of treatment by a homeopath, homeopathic methodologies and time required to observe changes; of recruitment of treatment and control arms; recruitment strategies and venues; recruitment of a representative ADHD population; and deliverability of the intervention. Feasibility findings informed the methods used for the STAR pilot feasibility study.

Treatment by one homeopath was associated with improvements after 4 months, and increased improvements at 1 year. It was found that usual classical homeopathic methodologies were suitable as long as homeopathic remedies were frequently taken. A novel methodology based on isopathic prescriptions of perceived environmental stressors was found to be particularly effective where individually indicated (Fibert, 2015b). Recruitment of treatment participants was successful and feasible, but recruitment of control participants only recruited half the participants.

Recruitment via ADHD support groups and charities was successful where a positive and personal relationship was established with leaders. Recruitment via schools was ineffective, and recruitment from the NHS was not possible since ethical approval was not requested.

Recruitment of the 'at need' population was achieved by recruiting from agencies dealing with children in trouble, such as police support agencies and social services. It was a surprise observation that the few children involved with the criminal justice system at the start of treatment reduced their involvement.

Attending appointments was problematic for some participants, particularly the 'at need' group, but visiting patients in their own home did not improve attendance. Best venue was a clinic already known to the family such as an agency clinic. Worst venue was the family home where participants were frequently distracted or absent, had the TV on, it was costlier and less time efficient to the homeopath.

Taking homeopathic remedies was generally acceptable and well implemented, although some participants took remedies inappropriately, lost them, or stopped taking them after a while. Regular consultations allowed for adjustment and correction and were considered important for this population for these reasons. CPRS-R: L was found to be too long and in too small print for patients, but MYMOP was liked by carers and older children. Both CPRS-R: L and MYMOP appeared to be sensitive to change.

4.3.3 Implications of the methods used for future research

Treatment by a homeopath was feasible, but results must be treated with caution since outcomes were collected by carers, aware of their child's treatment status. 4 months was sufficient time to demonstrate results. Since results in the treatment group continued to improve, and given that lack of long-term effectiveness of current interventions is a problem, measurement of the long-term effectiveness of treatment by homeopaths is important.

Recruitment of controls was difficult and strategies to improve this need exploring. Delivery of the intervention was challenging. Using known venues, prioritising consistency, strategies to manage missed appointments, lost remedies, and increased understanding of ADHD may be helpful. Although less sensitive, the CPRS-R: S (10 items) may be a more suitable outcome measure than CPRS-R: L (80 items) due to its shorter length. Since it was observed that the intervention was associated with improved levels of criminality and anger, changes in these areas should be measured.

4.4 Summary

This chapter has systematically reviewed the research literature for homeopathy and ADHD. Results suggest that the generic homeopathic remedies valeriana and selenium homichord cannot be recommended as treatments for ADHD since there is no evidence they are efficacious. The remainder of the studies do suggest that individually tailored homeopathic remedies may be efficacious when implemented according to usual treatment protocols. One unusual homeopathic methodology (Sankaran methodology) may not be suitable, but another (Boenninghausen methodology) may be. Case series reports document that carers find treatment by homeopaths helpful.

Trials of homeopathy to date have prioritised the evaluation of the specific effects of a single element of this multi-component treatment. Trials investigating overall treatment effects in clinical settings have been neglected (Witt, et al., 2012) despite being recommended. This review has highlighted the limitations of explanatory trial designs to provide useful information for stakeholders as to whether treatment by homeopaths might be helpful. There is a fundamental tension between internal and ecological validity, whereby studies representing optimum homeopathic treatment are at risk of bias and studies with reduced risk of bias are not representing homeopathic treatment.

Case Series results of treatment by homeopaths are of limited generalisability due to risk of selection biases (no randomisation); performance biases (homeopaths, researchers and/or participants not blinded); outcome assessment biases (outcomes measured by carers or clinicians who knew the child's treatment status); and Hawthorne effects).

Evidence generation has proceeded in the wrong order according to MRC recommendations to commence with trials exploring the *effectiveness* of complex interventions and only after effectiveness is established, explore the efficacy of separate elements. To assess whether homeopathic treatment might be helpful for people with ADHD, and provide useful information for stakeholders, good quality, well controlled studies of the effectiveness of treatment by homeopaths are required.

Chapter 5 Nutritional therapy

5.1 Background

This chapter describes the second intervention selected to be tested using the TwiCs design. It explores the evidence base and hypothesised mechanisms of action regarding nutritional interventions. It explains the rationale for describing the intervention as 'treatment by a nutritional therapist'.

The role of diet in ADHD has received considerably more research attention than the role of homeopathic treatment. It was first postulated in the 1970s by an American paediatrician, who found that his hyperactive patients improved with the elimination of salicylates, artificial colours and flavours, and petroleum based preservatives (Feingold, 1975).

Dietary factors in ADHD are researched in a variety of ways: by hypothesising explanations for the association between diet and ADHD; by exploring the association of poor diet with ADHD and exacerbation of symptoms when certain foods are introduced; and by exploring whether ADHD symptoms might be improved by making positive changes to the diet. This chapter will review the evidence from these three perspectives, with more systematic exploration of the latter category, as being most related to this intervention focussed study.

5.2 Hypotheses for the association between diet and ADHD

Several theories have been proposed to explain the association between diet and hyperactivity: poor diet, metabolic and/or mitochondrial dysfunction, immune-mediated hypersensitivity, gastro-intestinal inflammation and/or gut sensitivity, abnormality of fatty acid metabolism, and amino acid deficiency (Pellow, Solomon, & Barnard, 2011). However, while some neuro-imaging studies show anatomical differences, findings are inconsistent.

It is likely that both a lack of available nutrients and an inability to assimilate available nutrients optimally are implicated in the dietary association with ADHD. It is suggested that people with ADHD have a higher need for nutrients for optimal brain functioning which is exacerbated by the fact that they are consuming diets depleted in nutrients (Rucklidge & Johnstone, 2016).

5.2.1 Poor diet and the expression of psychiatric symptoms

Diet-related deficiencies and/or malabsorption of nutrients can result in the expression of psychiatric symptoms (Kaplan, Rucklidge, Romijn, & McLeod, 2015). Poor diet and resultant nutrient deficiencies may lead to oxidative stress and altered neurone plasticity. Deficiencies

of zinc, magnesium, glutathione, and/or omega-3 fatty acids, for instance, have been linked to poor concentration, memory, and learning problems (Dufault, Schnoll, & Lukiw, 2009). One theory posits that B group vitamins have a similar molecular structure to dopamine agonists such as methylphenidate - which inhibit the dopamine transporter (DAT) function, thus increasing dopamine at the synapse (Shaw, Rucklidge, & Hughes, 2010). B group vitamins may work together with minerals such as zinc, to inhibit DAT function (Lepping & Huber, 2010).

5.2.2 Metabolic and/or mitochondrial dysfunction

Neurotransmitters go through many metabolic steps to ensure synthesis, uptake, and breakdown, requiring enzymes dependent upon multiple coenzymes. Ames found that inborn errors of metabolism reduce the binding affinity of enzymes, which lowers the rate of metabolic reactions and hinders the synthesis and function of neurotransmitters (Ames, Elson-Schwab, & Silver, 2002).

Energy metabolism of neurons and glia cells (under the direct control of mitochondria), is highly dependent on the availability of a range of nutrients (McNally, Bhagwagar, & Hannestad, 2008). For example, magnesium, calcium, and several B vitamins are required as cofactors in the degradation of blood glucose via glycogenesis, and for aerobic metabolism in the respiratory chain in the mitochondria (Huskisson, Maggini, & Ruf, 2007).

Mitochondrial disorders are characterized by decreased production of adenosine triphosphate (ATP) the source of all cellular energy. Brain tissue in particular requires high levels of ATP for metabolism, including for the production of neurotransmitters. Manufacture of ATP may be compromised in ADHD (Gardner & Boles, 2005; Russell, et al., 2006; Young, 2007).

5.2.3 Immune-mediated hypersensitivity

Exposure to sensitising foods can increase inflammatory mediators and neuropeptides in the blood. Hypersensitive children may show symptoms of irritability, sleep disturbances and hyperactivity-impulsivity (Pellow, Solomon, & Barnard, 2011; Pelsser, Buitelaar, & Savelkoul, 2009). Stevenson (2010) suggested that some children with ADHD may have alterations in histamine genes, impacting their response to certain food additives. The function of the histamine receptor is known to affect hyperactivity levels in animals and influence dopamine release in the prefrontal cortex (Stevenson, 2010).

5.2.4 Gastro-intestinal inflammation and/or gut sensitivity

The gastrointestinal tract is one of the most energy-dependent and vulnerable organs. Its integrity is essential for proper nutrient absorption and function. Compromised gut flora

may lead to proliferation of opportunistic, pathogenic bacteria, viruses and fungi in the digestive tract, producing toxic substances which risk being absorbed into the blood stream and carried to the brain (Wilson & Tyburski, 1998; Samonis, et al., 1994). Mental disorders such as depression and anxiety have been found to be comorbid with celiac disease (Jackson, Eaton, Cascella, Fasano, & Kelly, 2012), and a growing body of research suggests that inflammation may play a role in psychiatric illness (Kaplan, Rucklidge, Romijn, & McLeod, 2015; McNally, Bhagwagar, & Hannestad, 2008).

5.2.5 Abnormality of fatty acid metabolism or lack of dietary essential fatty acids

Either abnormal fatty acid metabolism or a lack of essential fatty acids are postulated to be implicated in ADHD. A lack of fatty acids might impair communication between cells, leading to cognitive deficit (Pellow, Solomon, & Barnard, 2011). Fatty acids are essential for the flexibility of cell membranes. The myelin sheath, which insulates every neuron in the brain, consists of 75% phospholipids, with each molecule having an attached saturated and unsaturated omega-3 or omega-6 fatty acid. Their ratio is found to be a marker of health status. The brain and nervous system depend heavily on them, especially during childhood, which is a critical development period. Dietary deficiency during this time may increase the risk of developing ADHD-type symptoms (Haag, 2003).

Abnormalities of dopamine neurotransmission are associated with ADHD, and the functioning of neurotransmitters and receptors influenced by the lipid content of membranes. Omega-3 fatty acids, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), appear to improve neurotransmitter reception in the brain. DHA, in particular, protects neurons and glia by maintaining neural plasticity via induction of brain-derived neurotrophic factor (BDNF), a protein formed within the brain.

Modern grain based western diets have a fatty acid balance of 20 (omega 6):1 (omega 3), compared with 2: 1 in pre-agricultural diets based on animal and marine products, plants, nuts and seeds. This imbalance is considered to be a risk factor for ADHD. ADHD children may also have an inability to metabolize essential fatty acids (EFAs) correctly and frequently present with symptoms of EFA deficiency symptoms, which include dry hair and skin, eczema, recurrent infections, increased thirst and behavioural problems, temper tantrums, learning, health and sleep problems (Burgess, Stevens, Zhang, & Peck, 2000).

5.2.6 Amino acid deficiency

Amino acids are the building blocks of proteins, as well as precursors for most of the neurotransmitters in the brain. Certain amino acids need to be taken in through the diet; and low protein diets may foster amino acid deficiency symptoms (Pellow, Solomon, & Barnard, 2011). Many of the amino acids needed by the body to manufacture neurotransmitters,

such as phenylalanine, tyrosine, and tryptophan, are found to be low in the blood of adults and children with ADHD (Dufault, Schnoll, & Lukiw, 2009; Bornstein, Baker, & Carroll, 1990). Deficiencies of these neurotransmitter precursors, together with their vitamin and mineral cofactors, may result in ADHD-type symptoms (Harding, Judah, & Gant, 2003).

5.2.7 Mineral deficiency

Deficiencies in zinc, iron, calcium, magnesium, and selenium have been found in children with ADHD (Dufault, Schnoll, & Lukiw, 2009; Kozielec & Starobrat-Hermelin, 1997). For example, high levels of copper and a disturbance in the zinc: copper ratio were found in many ADHD children (Viktorinova, Trebaticka, & Paduchova, 2009). Zinc and iron are associated with dopamine metabolism, so a deficiency may be associated with impairment in dopaminergic transmission.

Consumption of certain artificial food additives can lead to nutrient deficiencies, particularly of zinc, in some individuals, which may exacerbate anxiety and conduct disorder problems (Oner, Oner, & Bozkurt, 2010; Pellow, Solomon, & Barnard, 2011). Furthermore exposure to metals such as lead, cadmium, mercury and aluminium have been linked to ADHD, and minerals such as zinc are needed to help metabolize and eliminate heavy metals (Dufault, Schnoll, & Lukiw, 2009).

5.3 Associations between poor diets and ADHD

Negative dietary factors found to be implicated in ADHD are: consumption of artificial food additives (Nigg, Lewis, Edinger, & Falk, 2012; Schab & Trinh, 2004); food sensitivities (Pelsser, Frankena, Toorman, & Rodrigues Pereira, 2017); trace element deficiencies (Hurt, Arnold, & Lofthouse, 2011), including iron (Cortese, Angriman, Lecendreux, & Konofal, 2012); fatty acid deficiencies (Schuchardt, Huss, Stauss-Grabo, & Hahn, 2010); a 'Western' style of diet (Howard, et al., 2011); poor nutrition generally (Melchior, et al., 2012); and malnutrition in infancy (Galler, et al., 2012), whereby children malnourished in the first six months of life were found to be at greater risk for ADHD symptoms 30 years later compared with children not exposed to such risk.

Unhealthy diets such as those high in saturated fats, refined sugars, and processed food and low in fruit and vegetables are associated with a higher incidence of ADHD (Howard, et al., 2011). Howard found that a population-based cohort of 14-year olds consuming a 'Western' diet (high intake of total and saturated fats, refined sugars, and sodium, and low intake of omega-3 fatty acids, fibre and folate), had higher rates of ADHD.

Meta-analyses conclude that artificial dyes and preservatives (sodium benzoate in particular), can trigger hyperactivity and inattentiveness, with younger children more prone than

older children, and that the greater the exposure the greater the effect found (Schab & Trinh, 2004). A relationship between certain food additives and exacerbation of ADHD like symptoms was found in 3-year olds (Bateman, et al., 2004) and 8–9 year olds (McCann, Barrett, & Cooper, 2007). An association between low omega-3 levels and having ADHD has also been found (Hawkey & Nigg, 2014).

Recently a relationship has been found between lower adherence to the Mediterranean diet and ADHD diagnoses (Ríos-Hernández, Alda, Farran-Codina, Ferreira-García, & Izquierdo-Pulido, 2017). The research team postulated that the relationship between poor diet and ADHD is bi-directional in that those with attention deficits, impulsive tendencies and difficulties using long-term motivators to inform short-term decision making, may make poorer food choices than those without.

Foods consumed today may not have the same nutrient composition as 50–100 years ago: for example, the mineral composition of 20 fruits and vegetables grown in the 1940s compared to the same fruits and vegetables grown in the 1990s showed significant reduction of four minerals in the tested vegetables, and three minerals in the tested fruits (Mayer, 1997). Furthermore, it is suggested that high yield crops produced with fertilizers, irrigation, and other environmental manipulations contain reduced nutrient concentrations (Davis, 2009).

Glyphosate has been specifically implicated in the depletion of minerals in plants (Bellaloui, Reddy, Zablotowicz, Abbas, & Abel, 2009), and manganese in cows (Samsel & Seneff, 2015). It has been postulated that increases in autism are associated with increased glyphosate usage it being “the only pesticide whose usage rates have gone up exactly in step with the rise in autism, and it is the most used herbicide on the planet” (Beecham & Seneff, 2016). Animal studies suggest that it induces impaired thyroid function. Neurological diseases can be explained by manganese deficiency (Samsel & Seneff, 2015).

5.4 Improving ADHD using nutrition

It is suggested that single nutrient interventions do not have adequate impact on the complex array of biochemical pathways that may be aberrant in ADHD. Furthermore, administration of one nutrient may cause an imbalance in other nutrients; and one nutrient is unlikely to resolve all vulnerabilities (Rucklidge, Johnstone, & Kaplan, 2009).

This section systematically reviews the research evidence for the effectiveness of nutritional interventions to improve ADHD symptoms. Studies with any type of comparator were included if they compared the effects of any or all aspects of a nutritional intervention such as: excluding food allergens, food chemicals, individually identified food substances or commonly provoking substances in normal diets; adding single supplemental nutrients such

as polyunsaturated fatty acids (PUFAs), zinc or magnesium; adding multi-nutrients; or a nutritional approach amalgamating any or all of these.

5.4.1 Search methods for the literature review

Web of science, Cochrane and google scholar were searched using the search terms ADHD AND nutrition AND meta-analysis OR systematic review OR RCT. A nutrition website (https://www.fabresearch.org) was also searched. Inclusion criteria were: all published primary studies of efficacy and effectiveness, randomised, quasi randomised, not randomised, cohort studies and case studies greater than N=1. Studies could include any aspect of nutrition. Trials could be of any duration, and participants of any age, including adults.

Studies could measure ADHD symptoms as a primary or a secondary measure. They could use any comparator, (eg placebo, treatment as usual, baseline or another intervention) and any outcome measure: validated or non-validated; self, carer, clinician or teacher-rated; specific measure of ADHD or generalised improvement rating, measure of wellbeing, or quality of life; measurement of accompanying symptoms such as anxiety, anger, opposition, or school performance. Exclusion criteria were editorials, commentaries and studies with no outcome measurement.

The level of evidence available was considered. Meta-analyses and systematic reviews were considered first. If no systematic reviews were found, individual RCT evidence was considered next. Where no RCTs had been conducted, then lower level evidence was described.

5.4.2 Search results

Seventeen meta-analyses were found in twelve articles. Seven investigated the effects of poly-unsaturated fatty acids (PUFAs) (Gillies, Sinn, Lad, Leach, & Ross, 2012; Bloch & Qawasmi, 2011; Puri & Martins, 2014; Hawkey & Nigg, 2014; Sonuga-Barke, et al., 2013; Cooper, Tye, Kuntsi, Vassos, & Asherson, 2015; Pelsser, Frankena, Toorman, & Rodrigues Pereira, 2017). One examined the effects of sugar (Wolraich, Wilson, & White, 1995). Four examined the effects of artificial food colour elimination (Sonuga-Barke, et al., 2013; Pelsser, Frankena, Toorman, & Rodrigues Pereira, 2017; Nigg, Lewis, Edinger, & Falk, 2012; Schab & Trinh, 2004). One examined the effects of the Feingold diet (Kavale & Forness, 1983). Four examined the effects of the 'few foods diet' (Pelsser, Frankena, Toorman, & Rodrigues Pereira, 2017; Sonuga-Barke, et al., 2013; Benton, 2007; Nigg, Lewis, Edinger, & Falk, 2012).

Some meta-analyses included uncontrolled and un-blinded studies, some amalgamated different types of diet interventions, and one included studies of the 'few foods diet' not specifically aimed at children with ADHD (Pelsser, Frankena, Toorman, & Rodrigues Pereira,

2017). Including just interventions conducted on children with ADHD using randomised controlled trial designs reduced the number of analyses to four of artificial colours (Sonuga-Barke, et al., 2013; Schab & Trinh, 2004; Nigg, Lewis, Edinger, & Falk, 2012; Pelsser, Frankena, Toorman, & Rodrigues Pereira, 2017); two of the 'few foods diet' (Sonuga-Barke, et al., 2013 & Benton, 2007) and three of PUFAs (Sonuga-Barke, et al., 2013; Pelsser, Frankena, Toorman, & Rodrigues Pereira, 2017; Gillies, Sinn, Lad, Leach, & Ross, 2012).

No meta-analyses or systematic reviews were found of individual or multi-nutrient supplementation or of a total nutritional approach. Therefore reviews by Stephenson (2014) (for the European ADHD Guidelines Group), by Rucklidge (2009), and Pellow (2011) were used to extract information regarding individual and multi-nutrient supplementation research.

Fatty acids (PUFAs)

The PUFAs were given for between four and 16 weeks, and consisted of omega-3 PUFA, omega-6 PUFA, or a combination of both.

Effect sizes found in meta-analyses were small. Pessler, (2017) found effect sizes of 0.17 for parent ratings, and -0.05 for teacher ratings. Sonuga-Barke, (2013) found an effect size of 0.21 (most proximal measurement) and 0.17 when restricted to probably blinded assessment. Gillies (2012) also found an effect size of 0.17 in blinded parent rated symptoms. Teacher ratings of overall ADHD symptoms found an effect size of 0.05.

A range of combinations of fatty acids were tested which makes it problematic to estimate the benefits of specific fatty acids. Researchers drew different conclusions on the differential efficacy of Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), Gamma-linolenic acid (GLA) and combined omega-6 and omega-3 PUFA supplementation. Some researchers suggest a combination of EPA, DHA and GLA is most likely to be efficacious (Hurt, Arnold, & Lofthouse, 2011; Schuchardt, Huss, Stauss-Grabo, & Hahn, 2010). Whilst others suggest a combination of EPA and GLA, without DHA (Puri & Martins, 2014).

Few food diets

The restricted elimination diets tested varied. Three studies tested few foods diets by giving children food challenges while on a few foods diet (Boris & Mandel, 1994; Carter, et al., 1993; Egger, Carter, Graham, Gumley, & Soothill, 1985), and four studies tested few foods diets against control diets (Kaplan, McNicol, Conte, & Moghadam, 1989; Pelsser et al., 2009; Pelsser et al., 2011; Schmidt et al., 1997).

Some diets only removed additives (Boris & Mandel, 1994; Kaplan, McNicol, Conte, & Moghadam, 1989; Schmidt, Mahle, Michel, & Pietz, 1987). Others were individually tailored

restricted elimination diets. Egger et al. removed foods found to be affecting individual children, which included cow's milk, wheat flour, citrus fruit, eggs, artificial colourings and preservatives (Egger, Graham, Carter, Gumley, & Soothill, 1985). Pelssler's diet consisted of water, rice, turkey, lamb, lettuce, carrots, pears, and other whole foods that are unlikely to cause allergic reactions (Pelsser, et al., 2011). Carter et al. tested a diet consisting of vegetables, fruits, rice and meat (Carter, et al., 1993).

Meta-analyses of these elimination diets differ widely in their effect size estimation, and vary dependent on whether blinded or unblinded assessments are considered. Pelsser has conducted two analyses (2011 & 2017). She found an effect size of 1.2 in 2011, and 0.51 to 0.80 in 2017 when only blinded RCTs were included for analysis. Nigg (2012) found a smaller effect size of 0.29; and Sonuga-Barke et al., (2013) found an effect size of 1.48 which fell to 0.51 when analysis was restricted to assessments made by probably blinded raters.

Trials were heterogeneous. Designs were a mix of cross-over and parallel group RCTs. Interventions varied in how strictly food elimination was applied. Results were influenced by two extreme SMDs from the same research group (Pelsser, Buitelaar et al., 2009; Pelsser et al., 2011) where concerns were raised over the blinded assessments (Adesman, 2011; Barkley, 2012). Concerns were due to the fact that the blinded assessments, whilst performed by a masked paediatrician, were partly based on information provided by parents who were not blinded. The primary outcome measures in these studies were based on parent and teacher reports which could not be blinded as they had to supervise the food intake of the child and knew whether the child was following an elimination diet.

Food colourings

Trials excluded certified food colours or implemented Feingold-type diets (described in 5.1). Results from the four meta-analyses varied. Sonuga-Barke (2013) found an effect size of 0.42. Pessler, (2017) found effect sizes varying from 0.08 (teacher ratings) to 0.44 (parent ratings). Nigg (2012) found effect sizes varying from 0.12-0-18 (adjustment for publication biases). Schab & Trinh (2004) found effect sizes of 0.28 to 0.21 when lowest quality trials were excluded.

The effects found are attenuated by the fact that in some trials, selected participants showed some prior intolerance (Stevenson, et al., 2014). In the three studies of children not already suspected to be responders to food colours (Conners, Goyette, Southwick, Lees, & Andrulonis, 1976; Harley et al., 1978; Williams, Cram, Tausig, & Webster, 1978) a SMD of 0.24 was found (Sonuga-Barke, et al., 2013). This suggests that the value is greatest for those sensitive to food colours, but the approach may also be more broadly applicable.

It is unclear whether findings are still relevant, since studies were conducted before 2007, when the use of artificial food colourings was reduced in the UK in response to a voluntary ban requested by the Food Standards Agency (http://food.gov.uk/policy-advice/additivesbranch/foodcolours/colourfree/#.Uoi-FxrxqjW).

Multi-nutrients

Studies of multi-nutrients for ADHD are mostly small, of poor quality, and/or not measuring blinded outcomes or ADHD symptoms (Kaplan, Fisher, Crawford, Field, & Kolb, 2004; Harding, Judah, & Gant, 2003; Patel & Curtis, 2007; Sinn & Bryan, 2007). For example, the study by Kaplan was a small open-label study of eleven children with a variety of psychiatric disorders including ADHD (5/11), who took *EMPowerplus* (consisting of 14 vitamins including vitamins D, E, H, and a range of B group vitamins; 16 minerals including calcium, iron, magnesium, and zinc; and three amino acids (methionine, phenylalanine, and glutamine). After 16 weeks all children were rated as significantly improved in aggression, attention, anxiety, delinquency, and mood (Kaplan, Fisher, Crawford, Field, & Kolb, 2004).

Two double-blinded RCTs have recently been conducted by the same research group (Rucklidge, Egglestone, Johnstone, & Frampton, 2017; Rucklidge, Frampton, Gorman, & Boggis, 2014). One in adults with ADHD also tested the efficacy of *EMPowerplus* (Rucklidge, Frampton, Gorman, & Boggis, 2014). Clinically significant improvements in inattention and hyperactivity/ impulsivity were found (effect size 0.46 to 0.67). The longer patients remained on the micronutrients, the better the effect found.

Most recently Rucklidge (2017) conducted a blinded RCT of medication-free children (n = 93) with ADHD (7– 12 years) who were given micronutrients or placebo for 10 weeks. Intention-to-treat analyses favoured micronutrient treatment on the Clinical Global Impression scale (effect size 0.46). Clinician, parent and teacher ratings of ADHD symptoms did not show any group differences (effect size 0.03–0.17), although greater improvements in emotional regulation, aggression and general functioning were found (effect size 0.35–0.66).

Single supplements

Three RCTs of zinc supplementation in ADHD have been conducted. Significant effects were seen in two trials (SMD 1.06) (Bilici, et al., 2004) (Akhondzadeh, Mohammadi, & Khademi, 2004), but not in the third (SMD = 0.02) (Arnold, et al., 2011).

Bilici et al.'s 12-week trial found a significant improvement on ADHD rating scales for hyperactivity, impulsivity and socialization, but not for attention. Akhondzadeh et al. conducted a 6-week, double-blind RCT comparing zinc supplementation with placebo in 44 children taking methylphenidate. Those receiving zinc plus methylphenidate showed significantly better

improvements on the DuPaul ADHD Rating Scale than those in the placebo group. Arnold randomly assigned 52 children aged 6–14 to zinc supplementation or matched placebo for 13 weeks with equivocal results.

Two RCTs have been conducted of supplementation with carnitine and results differed. Van Oudheusden & Scholte, (2002) found significant effects for carnitine (SMD = 1.38 (parent rating), 0.86 (teacher rating)) whilst Arnold et al. (2007) did not (SMD = 0.23).

Two studies have examined the effects of iron supplementation on children with ADHD. One non-randomised study where 14 boys with ADHD were given iron for 30 days showed a significant increase in serum ferritin levels, and a decrease in parent but not teacher ratings (Sever, Ashkenazi, Tyano, & Weizman, 1997). An RCT of 23 children with low serum ferritin levels (Konofal, et al., 2008) had similar results, but also found significant improvement on two clinician-based scales (the ADHD Rating Scale, and the Clinical Global Impression – Severity score).

The results of some further trials of single supplements are now summarised. Small beneficial effects of low doses of caffeine were found in six participants (Barry, Christopher, & Sloman, 1981). Significant effects of tryptophan (which can increase synthesis of serotonin) were found on parent (SMD = 0.99), but not teacher ratings (SMD = 0.03) (Nemzer, Arnold, Votolato, & McConnell, 1986).

St John's Wort has been noted to increase the levels of serotonin, dopamine and norepinephrine in the brain. In an 8-week RCT (Weber, et al., 2008), 54 children with ADHD were randomized to St John's wort extract three-times daily or a placebo. No significant difference was found in the ADHD Rating Scale-IV or Clinical Global Impression Improvement Scale, although a SMD of 0.56 was measured. One small open trial did however, find improvement in ADHD symptoms (Niederhofer, 2010).

Supplementation with vitamin B6 and magnesium was found to increase serotonin levels and reduce hyperactivity in ADHD in a study of 40 children who took the supplements for 8 weeks. Hyperactivity symptoms returned a few weeks after treatment was stopped (Mousain-Bosc, Roche, & Polge, 2006). Supplementation with a low/high dose of vitamin B6 alone was compared with a low/high dose of methylphenidate and with placebo, in six hyperactive children over a 21-week period. Nonsignificant trends suggested that B6 and methylphenidate were more effective than placebo but B6 alone was not (Coleman, Steinberg, & Tippett, 1979).

In a nine-week RCT of S-Adenosyl-L-Methionine (the active form of methionine, required for the synthesis of norepinephrine, dopamine, and serotonin), 75% of adult ADHD patients showed improvement (Shekim, Antun, & Hanna, 1990). An RCT of 74 children found that a

daily dose of Dimethylaminoethanol (an acetylcholine precursor aiding memory, learning, and improved mood) for three months was as effective as Ritalin (Lewis & Young, 1975).

No effects were found of vitamins (Haslam, Dalby, & Rademaker, 1984), bark extracts (Trebaticka, et al., 2006), tyrosine (Nemzer, Arnold, Votolato, & McConnell, 1986), or aspartame (Shaywitz, et al., 1994).

A global nutritional approach

A global nutritional approach is defined as being a combination of nutritional approaches: supplementation, elimination and eating a healthy diet. No RCTs were found examining the effectiveness of a global nutritional approach, however, in 2007, Curtis and Patel conducted a preliminary study of 10 patients diagnosed with ADHD and autism. Over three to six months, they eliminated problematic foods (such as gluten, casein, and food additives); added more whole foods and supplements (such as probiotics, B group vitamins, and omega-3 fatty acids); and reduced the children's exposure to toxins, including house-dust mites, mould-causing moisture, tobacco smoke, and pesticides.

They concluded that children "showed significant improvement in many areas of social interaction, concentration, writing, language, and behaviour", and suggested that "until we know more, the bundling approach appears to be the best use of the environmental-medicine arsenal". To date this is the only (small) study of such a global nutritional approach (Patel & Curtis, 2007).

5.5 Summary of the literature review

The three most researched interventions are few foods diets, artificial food colour elimination and PUFA supplementation. Of these, the effect sizes of artificial colour elimination and PUFA supplementation are probably too small to contribute significantly alone, but may contribute to a multi-modal approach. Artificial food colour elimination in children with sensitivities may be particularly helpful. Trials of vitamins, minerals, amino acids, single and multiple nutrients show varied results ranging from negligible to modest, which tend not to be replicated. More studies are required before conclusions can be reached on the value of any of the supplements tested thus far.

Researchers concur that the few foods diet may offer novel treatment opportunities, although further large-scale studies are needed on unselected children, including blinded assessments and assessments of long-term outcomes (Stevenson, 2014).

A substantial and growing body of research suggests that diet, both in terms of eliminating certain additives, eating healthy foods, and supplementing with an array of vitamins and

minerals, may play a role in the treatment of ADHD. Single nutrient interventions are probably not effective for improving ADHD symptoms. It is suggested that this may be because the administration of one nutrient can cause an imbalance in others; and/or because supplementing with one nutrient alone is unlikely to correct all the vulnerabilities present in such a complex and heterogeneous disorder as ADHD (Rucklidge, 2016).

Symptom response to dietary change is likely to differ among individuals, and this needs to be considered when designing trials and when interpreting trial results. For example, in some studies, children are recruited on the basis of previous responses to foods.

5.6 The safety of nutritional interventions

Sonuga-Barke et al. (2013), found that 6 of 12 RCTs on supplementation with PUFAs appraised adverse events. The events noted were minor episodes of symptoms such as dyspepsia (Manor, et al., 2012), diarrhoea (Gustafsson, et al., 2010) and occasional nose bleeds (Milte, et al., 2012). The studies on artificial food colour elimination and restricted elimination diets did not formally report on adverse effects, with the exception of Pelsser et al. (2011), where no incidents were found.

5.7 Stakeholder position on a nutritional approach

Current NICE guidelines (2008) say that health care professionals should stress the value of a balanced diet, good nutrition and regular exercise. They should ask about foods or drinks that appear to influence hyperactive behaviour as part of the clinical assessment of ADHD. If there is a clear link, then they should advise carers to keep a diary of food and drinks taken and ADHD behaviour. If the diary supports a relationship between specific foods and drinks and behaviour, then a referral to a dietitian should be offered. Further management should be jointly undertaken by the dietitian, mental health specialist or paediatrician, and the carer and child.

The recently updated NICE guidelines (https://www.nice.org.uk/guidance/ng87/chapter/Recommendations#dietary-advice) make several negative recommendations. Heath professionals are advised not to advise elimination of artificial colouring and additives from the diet; not to advise or offer dietary fatty acid supplementation; and not to advise a few foods diet, because there is no evidence about the long-term effectiveness or potential harms, and only limited evidence of short-term benefits.

To inform this update, workshops were conducted, which I attended. Elimination diets and supplementation with PUFAs were considered. For the assessment, most studies of elimination diets were excluded (4 because of an incorrect population; 3 because of an incorrect

comparator; 13 due to incorrect study design (not RCT or systematic review); 2 with a treatment duration under 2 weeks; and 4 not in English), which left only two studies by a single author (Pessler 2009 & 2011). Their review of PUFAs found no clinically important differences over placebo in ADHD symptoms in the short and long-term.

Considerable frustration was expressed by the attending clinicians and lay reviewers at the workshop about the proposed lack of dietary advice in an area where in their experience it is of clinical benefit. The attendant NICE guideline reviewers highlighted the need to retain stringent protocols using GRADE (described in section 3.3.5), but acknowledged that such frustrations are a common problem.

A post-workshop response stated that "the Committee agreed that the elimination of artificial colours and preservatives is an important issue and warrants specific research on its long-term effectiveness in the management of ADHD. The Committee have therefore added a research recommendation that a randomised controlled trial is conducted to address this question. The Committee noted that dietary interventions can be associated with harms, burdens on families, and costs. Therefore the Committee were unable to recommend interventions without clear evidence of benefit for children and young people with ADHD." (www.nice.org.uk/.../documents/workshop-notes-2).

5.8 Trial design implications

5.8.1 Identified issues with current research

Nutrition is in particular need of testing as a complex intervention. Assessors have criticisms of the evidence base which preclude them from making positive dietary recommendations. The majority of NICE dietary recommendations (3/5) are negative. NICE furthermore have concerns regarding burden, cost and harms.

The European ADHD guidelines group (Stevenson, 2014) also found the evidence insufficient regarding impact on core ADHD symptoms. This was mainly because some studies measure non-ADHD outcomes; reviews tend to include trials using nonrandomised designs or in non-ADHD samples; and unblinded assessments are often used. They also raise the problem of generalisability since in some studies children were recruited on the basis of previous responses to foods.

Blinded, placebo-controlled RCTs have tested the efficacy of specific nutritional interventions, but no RCTs have yet tested the effectiveness of a total nutritional approach. Considerable research, at considerable cost would be required to generate sufficient evidence for NICE of the efficacy of each specific dietary intervention. Furthermore, nutrients interact with each other, and, it is unlikely that any single nutrient or dietary approach will prove to be a panacea to improve ADHD.

Trials of nutritional interventions tend to be short, like trials of pharmaceutical medication. This may not be measuring optimum effects because it is likely that the dietary interventions will be more effective if sustained over a long period of time. It is suggested that if diet changes are terminated, ADHD behaviours return. The longest trial of the 'few foods diet' was 5 weeks (Pelsser, 2009 & 2011); of artificial colour elimination 8 weeks (Adams, 1981); of PUFAs 4 months (Milte, 2012; Stevens, 2003; Voigt, 2001) (in Sonuga-Barke, 2013).

5.8.2 Recommendations for future research

Collectively research suggests that a nutritional approach is warranted: nutrient supplementation shows some, if inconsistent effects; few foods diets show more consistent evidence of improvements; and there is evidence showing aggravation of ADHD symptoms with poor diets.

Systematic reviewers have called for high quality, bias-proof clinical trials addressing the effects of dietary exclusions and supplements on children's behaviour (Sonuga Barke, 2013; Stevenson, 2014). The European ADHD guidelines group recommend that in the future, children should not be recruited on the basis of previous responses to food stuffs; studies should include blinded observations; they should control for nonspecific treatment effects; and the course of changes in response to treatment over the medium and long-term should be established (Stevenson, 2014). Measurement of a broader range of child, carer, and family-related functional outcomes has also been called for (Kidd, 2000).

5.8.3 The suitability of the TwiCs design

The TwiCs design addresses some of the design recommendations listed above. Broad recruitment criteria allow for maximum generalisability, with all children with ADHD randomised to be offered the intervention rather than just those with food sensitivities. Measurement of the acceptability of the intervention can provide useful information because elimination diets are difficult to manage: previous studies were of children aged 4-8 because it was thought that older children may not be compliant.

Reviewers specifically called for measurement of blinded outcomes, for non-specific effects to be controlled for and for long-term outcomes to be measured. Collection of observations from teachers can provide blinded assessment. Measurement of long-term outcomes is a feature of the design. But non-specific treatment effects are not controlled for using this design. The rationale for not doing so was discussed in section 3.1.

Collecting real-world outcomes such as school performance, criminality, exclusion and well-being measures a broad range of functional outcomes.

5.8.4 Rationale for treatment by a nutritional therapist

Testing the effectiveness of a global nutritional approach, as opposed to multiple individual trials of separate nutrients or interventions, is indicated for practical and scientific reasons. One trial is much cheaper than multiple trials. Treatment by nutritional therapists includes individually tailored exclusion of identified aggravating substances, and/or supplementation. An individualised approach is indicated since sensitivity to substances is found in some rather than all those with ADHD. An initial study suggests this is a viable approach (Curtis & Patel, 2007). Arguably, improvements might be optimised by both eliminating aggravating factors and boosting nutritional deficits.

Regular consultations with a nutritional therapist would monitor safety and adequate nutrient intake, addressing concerns that children may not receive adequate nutrition. Nutritional therapists can document compliance, which is an important consideration. Regular consultations allow changes to be made gradually, and for each change to be consolidated before a new change is proposed. This may sustain momentum and provide an incentive to maintain dietary changes.

Professionals working in the field of nutrition have different titles: nutritionists, dieticians, and nutritional therapists being just three. Whilst there is considerable overlap between the professions, nutrition within the NHS is usually managed by dieticians, who are statutorily regulated, only advise where evidence is well established; and tend to advise on optimum generic nutrition, for example the healthy plate, rather than on an individualised basis. Nutritionists tend to work for public bodies in an advisory role (http://www.nutritionist-resource.org.uk). Nutritional therapists are considered complementary therapists, tend to work privately with individuals, take an individualised approach, and consider that dietary intervention can be used to prevent, mitigate or cure chronic disease (Kaput & Kaput, 2004). Nutritional therapists are not statutorily regulated but have their own code of ethics and procedures managed by the British Association of Nutritional Therapists (BANT).

Chapter 6 Methods.

6.1 Aims and Objectives of the pilot feasibility study

Aims

The long-term aim of the Sheffield Treatments for ADHD Research (STAR) project is to improve outcomes for children with ADHD, by developing a facility for efficiently and objectively testing multiple interventions for them over the long-term.

The aim of this thesis is to assess the feasibility of the TwiCs design to provide information to enable the evaluation of treatments for ADHD. Therefore the aim of the pilot feasibility study is to assess whether the TwiCs trial design can provide suitable information for stakeholders to enable evaluation of the clinical and cost effectiveness of some treatments for ADHD.

This was done by conducting a small-scale test of the methods and procedures: a three-armed internal pilot trial of the clinical and cost effectiveness of 2 treatments: (a) the offer of adjunctive treatment by homeopaths and (b) the offer of adjunctive treatment by nutritional therapists, compared to (c) treatment as usual. A further aim is to assess the acceptability, deliverability, clinical and cost effectiveness of the two treatments for children with ADHD.

Objectives

The objectives of this feasibility study are to:

- assess the feasibility of recruiting to time and target a cohort of children with a diagnosis of ADHD
- test the feasibility and acceptability of the study design
- test the feasibility, deliverability, safety, acceptability, clinical and cost effectiveness of the interventions
- assess the suitability, acceptability and deliverability of the outcome measures.
- inform the sample size calculation for the full trial.

Table 18 describes how these objectives will be met.

6.2 Approvals for the pilot feasibility study

6.2.1 Research governance sponsorship

In line with the Department of Health's Research Governance Framework for health care research studies (www.dh.gov.uk), the University of Sheffield was the research governance sponsor. The first version of the pilot trial conceived one arm as a trial of polyunsaturated fatty acids (PUFAs). When the University of Sheffield Research and Innovation services (RIS) were applied to, they recommended contacting the Medicines Health Regulatory Authority (MHRA) in case this arm might be considered a Clinical Trial of a Medicinal Product (CTIMP) and therefore require MHRA approval. The MRHA did indeed deem that the PUFAs were being tested as a medicinal product. Therefore to ensure that the study would not be classified as a CTIMP, with all the additional bureaucracy that would entail, the PUFA arm was substituted with 'treatment by a nutritional therapist'.

Sponsorship for the trial testing the effectiveness of treatment by nutritional therapists and treatment by homeopaths was received on 10/7/15. Additionally, the study was risk assessed by University of Sheffield Research and Innovation services (RIS) because it was a human-interventional study. It was assigned University Research Management System (URMS) number 143647.

6.2.2 Protocol for the pilot feasibility study

The trial protocol received Independent Scientific Review from Professor Heather Boon (University of Toronto); Dr Jack Parker (ScHARR, UoS) and Dr Val Harpin (Consultant Paediatrician, Sheffield NHS).

The trial was registered with the International Standard Randomised Controlled Trials registry, registration number 17723526. (http://www.isrctn.com/ISRCTN17723526) on 27/04/2015. It was subsequently published in the journal Pilot and Feasibility Studies (Fibert, Relton, Peasgood & Daley, 2018).

6.2.3 Ethical approval for the pilot feasibility study

Ethical approval was received from the University of Sheffield School of Health and Related Research (ScHARR) Research Ethics Committee (REC). An amendment was subsequently sought for the PUFA arm to be replaced with 'treatment by a nutritional therapist'. Further amendments were sought for questionnaires to be completed on-line, and consultations to take place in a variety of venues and modes, including on-line (Table 16).

Table 16. Ethical approval amendments

Version	Date	Amendment
1	30/4/15	
2	7/10/15.	PUFA arm replaced with 'Treatment by a nutritional therapist'
3	2/2/16	addition of an on-line questionnaire; addition of the SNAP outcome measure; addition of the option for therapists to conduct consultations on-line; an additional letter sent to GPs on recruitment of participants
4	28/4/16	addition of the offer of a £10 Boots voucher incentive for those who completed 6 months onwards questionnaires; the option to complete questionnaires by phone

The trial management team concluded that the study was not recruiting research participants identified from, or because of their past or present use of NHS services (HRA-decisiontools.org.uk), therefore National Health Service (NHS) REC approval was not sought.

6.3 Management of the pilot feasibility study

The trial was overseen by an independent steering committee chaired by Professor David Daley, University of Nottingham, and a management committee consisting of myself (Principle Investigator) and Dr Clare Relton (Public Health, ScHARR, UoS). The committee met 6-monthly and the management committee met monthly for the duration of the trial.

6.3.1 Recruitment to the STAR cohort.

Various recruitment strategies were explored. This included considering recruitment from ADHD facilities such as special schools, secure units, NHS facilities, and children engaged with nationally and locally funded support services. As no NHS approval was obtained, the STAR project recruited through a broad variety of non-NHS sources such as local authority based organisations, schools, university based events and listings, clinically relevant support groups, clinically relevant conferences, and social media.

A variety of modes of communication were used: public talks, face to face meetings, phone conversations, flyer distribution (Appendix 3), emails, letters, and social media.

Local Authority organisations

Application to advertise the project was made to Sheffield Parent Carers, an independent, local authority funded group of 1,000+ carers of children with disabilities including 150+ with ADHD. They agreed to post an advertisement in their newsletter and send an email to all members registering a child with ADHD.

Sheffield city council Multi Agency Support Teams (MAST) and the research office for children's services were applied to. MAST were too busy to consider the application, but the city council felt the trial met their concerns regarding appropriate management of safeguarding, data protection, and consenting children (Appendices 9 & 10). They requested that literature refer to 'carers' rather than 'parents' which was done. They were particularly positive about the trial design because children would not be offered the possibility of something they may not get. However, when the STAR project was presented to their 'Looked after children' committee (chaired by an NHS CAMHS paediatrician) the committee considered that NHS ethical approval was a pre-requisite.

Family Action Sheffield were approached. Sheffield City council contract Family Action Sheffield to run 10-week parenting programmes and conduct home visits for newly diagnosed ADHD families. Permission was gained from national Family Action to advertise the trial to families they work with. Two weeks after the STAR project started recruiting there was a breach of protocol, whereby a Family Action worker erroneously handed out flyers within CAMHS: Family Action workers sometimes work alongside NHS staff in NHS premises, but since NHS ethical approval had not been obtained, recruitment should not have occurred during combined sessions or on NHS premises. It was made clear to Family Action workers that the study does not have NHS REC approval.

The breach of protocol resulted in a challenge to the STAR project recruitment strategy. It was claimed that NHS approval is required for all children diagnosed with ADHD. This was refuted by ScHARR research ethics committee, University of Sheffield Research and Innovation services, and the chair of the steering committee, who all confirmed that NHS ethical approval was not a pre-requisite (see discussion section 9.1.1).

Schools

All maintained, private special schools, and mainstream schools with integrated special resource units in Sheffield were contacted if they specialised in: Autism and Communication Difficulties, Behavioural, Emotional and Social Difficulties, or Learning Difficulties and Complex Needs. They were sent an email describing the project, then visited, flyers left at reception, reception staff told about the project, and the offer made to speak with the Special Educational Needs Co-Ordinator (SENCO). If families recruited to the cohort provided the child's school details, when those schools were contacted they were asked to promote the study to any other pupils with ADHD.

(See Festival of the Mind below for further school-based activity).

University based events and listings

A variety of Sheffield University public engagement events were used to promote the STAR project (http://www.sheffield.ac.uk/ris/publicengagement). Before each event, Sheffield proximal ADHD support groups were told about the event, and details were posted on the STAR Facebook page.

An illustrated talk was given on a vintage bus in central Sheffield (http://www.sheffield.ac.uk/mobileuni). A keynote lecture for Holistic Health at the Hide hosted by Pending Coffee Sheffield was given. Talks were given at 24 hour Inspire, and Pint of Science, (http://www.sheffield.ac.uk/ris/publicengagement/festivals-and-other-opportunities/pint-of-science).

Information about the STAR project was circulated to staff and students at the University of Sheffield via University email lists. STAR joined the Sheffield Forum (www.sheffieldforum.co.uk) and placed an advertisement about the STAR project in the 'Disability and Carers' and 'Sheffield parenting' groups on the forum.

A Festival of the Mind (http://festivalofthemind.group.shef.ac.uk/) application linked the STAR project with Nathan Gordon, hip hop dancer, slam poet and stunt man. An award of £5,000 was received which enabled the creation of a performance and video entitled 'Lost Voices'. The poem (Appendix 12) was created based on material gathered by conducting workshops in schools and asking STAR project participants for their stories. All special schools and schools with special units in Sheffield were offered a workshop and two accepted. Participants were emailed and asked to contribute stories about their experiences of ADHD. Those who agreed were contacted by Nathan who listened to their stories. Lost Voices was performed on September 18th and 19th 2016 in Sheffield town centre https://www.facebook.com/starsheffieldADHD/videos/vb.514537418704645/677387002419685/?type=2&theater).

Newcastle University host an autism spectrum database (ASD-UK) with the aim of helping researchers recruit families to studies about ASD that may lead to advances in the care and treatment of children, and allowing families to take part in research that aims to answer important questions about autism spectrum disorders. A formal application to use this database was submitted.

Clinically relevant groups

A search on-line was made for local clinically relevant support groups and organisations, and the following groups contacted: the Sheffield Autistic Society, Autism plus, Little Rainbows (Doncaster), the Autism centre at Sheffield Hallam University, Sparkle Sheffield, Sheffield

Asperger's Children and Carers Together, (ACCT), Ray of Hope (Sheffield Children's Additional Needs Support Group). Where groups expressed interest, they were sent flyers, and linked with the STAR Facebook page.

Requests to advertise the STAR project were made to the directors of national groups: The Children's Sleep Charity (www.thechildrenssleepcharity.org.uk); the National Attention Deficit Disorder Information and Support Service (ADDISS) (www.addiss.co.uk); the Hyperactive Children's support group Network, (www.hacsg.org.uk); the Attention Deficit/Hyperactivity Disorder Online information service (www.adders.org); ADHD solutions (cmsms.adhdsolutions.org). Groups placed information about the STAR project on their websites.

The publications 'Autism Eye', 'What the Doctors Don't Tell You', and 'ADHD news' (the quarterly publication of ADDISS) were approached but did not agree to advertise the STAR project. Information about the STAR project and requests for participants were made to the professional bodies of the therapies being tested: the British Association for Nutritional Therapists (BANT) (bant.org.uk); and the Society of Homeopaths (SOH) (http://www.homeopathy-soh.org)

The UK Adult Attention Deficit group (AADD-UK) provide a list of ADHD support groups for adults and children throughout the UK (https://aadduk.org/help-support/support-groups/). From this list, relevant groups were emailed, including the newly opened Oxford ADHD Centre (www.oxfordadhdcentre.co.uk).

Conferences

The following conferences were attended and oral or poster presentations made (Appendix 15):

- World Federation of ADHD conference (Glasgow) (poster presentation) May 2015
- Homeopathic Research Institute (HRI) Conference (Rome) (oral presentation) June 2015
- Research Council for Complementary and Integrative Medicine (RCCM) Conference (London) 'Demonstrating the Value of Integrative Medicine' (poster presentation) June, 2015
- Centre for the study of Childhood and Youth (CCYT) 'Childhood and Food' Seminar (Sheffield) (oral presentation) February 2016
- RCTs in the Social Sciences (York) (oral presentation) September 2016
- Society of Homeopaths Annual Conference (Nottingham) (oral presentation) September 2016

In addition the following events were attended, and flyers distributed:

- the Homeopathic Medical Association Annual Conference April 2016
- NICE guideline ADHD (standard update) scoping workshop (London) December 2015
- NICE Nutrition Guidelines for ADHD workshop (Manchester) September 2015
- Food and Behaviour (FAB) Conference (Sheffield) October 2015
- Treating Autism Conference (Brunel University) (stand taken) June 2016

Social media

A STAR Facebook page was created with links to the on-line questionnaire, relevant events attended or spoken at, ADHD articles, STAR newsletters, Facebook pages of ADHD organisations ADHD/ASD SUPPORT GROUP - UK/I, ADHD action, ADHD comms, ADHD Richmond, ADHD matters, ADHD solutions, and ADHD South Yorkshire (www.facebook.com/starsheffieldADHD). BBC Sheffield presenters were contacted and Twitter and LinkedIn accounts used to advertise the STAR project.

6.3.2 Cohort inclusion and exclusion criteria

These were kept to a minimum to maximise external validity.

Inclusion criteria for the STAR cohort were children aged 5-18 (inclusive) with a carer reported diagnosis of ADHD and a carer reported Conners' Global Index (CGI) T score of at least 55, which denotes mild a-typicality (Table 17). All co-morbidities were eligible for inclusion and children could be participating in any other interventions for their ADHD.

Exclusion criteria to the STAR cohort were children below the age of 5 or adults over 18; children with terminal conditions such as cancer; families where English was not written or spoken (as the project does not have funds to provide a translation service at this stage).

Table 17. Interpretive guideline for Conners Global Index

T score	Percentile	Guideline
70+ 66–70	98+ 95–98	Markedly Atypical (Significant problem) Moderately Atypical (Significant problem)
61–65	86–94	Mildly Atypical (Possible problem)
56–60	74–85	Slightly Atypical (Borderline)
<30–55	<2–73	Average (Typical: Should not raise concern)

(Extracted from Conners. 2008)

Inclusion criteria for the pilot trial were a carer reported ADHD diagnosis and a carer reported CGI T score of at least 65, which indicates a significant problem.

Exclusion criteria for the pilot trial were children currently receiving treatment by a homeopath or a nutritional therapist; and children with CGI T scores below 55 (Table 17).

Emails were sent to families returning questionnaires whose child did not fulfil inclusion/exclusion criteria explaining the reason for the exclusion and thanked them for their interest.

6.3.3 Randomisation to the first pilot trial

Randomisation was performed by an independent statistician at ScHARR: Professor Mike Campbell. There were three stratifying factors in blocks of 6: age (primary school 5-11 / secondary school 12-18); medication status (yes/no); ADHD severity (T score 80+/under 80) (Table 17). These stratifying factors were selected since they were considered likely to influence treatment response. Age and ADHD severity may influence both treatment response and drop out, whilst medication status was selected since other research into a CAM therapy has suggested that those on medication may respond differently to those not on medication (Hong, 2016).

The randomisation list was housed in the locked drawer of another independent statistician at ScHARR: Dr Evangelos Kritsotakis. On recruitment to the cohort, age, ADHD T score, and medication status were extracted from the questionnaire. Participants fulfilling inclusion and exclusion criteria who consented to be contacted again were identified and their anonymised information sent to Dr Kritsotakis by email, who randomly assigned them to one of three groups: the offer of treatment by homeopaths; the offer of treatment by nutritional therapists; or treatment as usual. Each participant was allocated a randomly generated three-digit code, by which participants were subsequently identified. Those randomised to treatment as usual were not informed that they had not been selected for a treatment.

6.4 The offer of treatment

Those randomly selected to be offered a treatment were sent a letter (Appendix 6) offering them one year of treatment. The letter gave a brief description of the treatment and what to expect; a request to the carer to ask their child if they are happy to participate; a consent form to treatment, to be signed by both carer and child and returned in a pre-paid envelope; and an email address and telephone number as an alternate means of contact.

The PI then rang the selected participants a week later to ask if they had any questions, and if they wished to take up the offer (if their form hadn't yet been returned). If both carer and

child consented, they were told them the name of their designated therapist, and asked for their permission to pass on their contact details to that therapist. In the absence of a returned 'consent to treatment' form, carer and child's wish to participate on the telephone was taken as verbal consent, and the form completed at the first meeting with the therapist, who further explained what treatment will constitute, as befits usual practice. Appropriate marks by young children were taken as signatures.

Participants were rung and emailed at least three times each before being considered non-responders. Both non-responders and participants refusing the offer of treatment were sent outcome measures to complete as usual every 6 months.

6.5 Delivery of the interventions

Treatment by homeopaths, and treatment by nutritional therapists are not currently offered in routine health care by the NHS. Both interventions are generally paid for privately and delivered at complementary health clinics. Therefore eight therapists (4 nutritional therapists and 4 homeopaths) were initially recruited via Wellforce Integrated Medicine Clinic, which offers complementary therapies in Sheffield.

Both interventions (the offer of treatment by homeopaths and the offer of treatment by nutritional therapists) were offered to participants for a maximum of one year consisting of up to 8 appointments, resulting in up to 7 contact hours. Once participants had accepted the offer of a treatment, their contact details were given to the most proximal, available therapist, who then arranged a mutually convenient time, and venue/mode for a consultation. If therapists failed to make contact with a participant after 3 phone calls and 3 emails, that participant was deemed a non-responder.

Consultations took place in a variety of non-NHS premises (Wellforce Complementary Medicine Centre (Sheffield); Western House Consulting rooms (Barnsley), Beighton Lifestyle Centre (Sheffield), and patient's or practitioner's homes. They were delivered face to face, by telephone, or on-line. Consultations mirrored usual practice in that any missed appointments were rebooked, and venues, times between consultations, and number of consultations all varied.

Before the trial began, all therapists who were going to deliver the therapies attended workshops run by the PI. The workshops trained them in management of ADHD and how to recognise and respond to any serious adverse events (Appendices 9 & 10). All therapists completed the on-line Sheffield safeguarding children child protection course (Safeguardingchildrentraining@sheffield.gov.uk). Homeopaths were given training in a specific homeopathic methodology for treatment of exposure to environmental toxins, which had been found to be useful in the case series (Fibert, Relton, Heirs, & Bowden, 2016).

After each consultation, therapists completed a form (Appendix 2) which included the date, consultation number, MYMOP score, treatment summary and progress, and reported any adverse event. On the occasion of an adverse event, an additional form was completed (Appendix 9).

Therapists asked participants for their GP's details and permission to contact them. GPs were then sent a letter explaining that their patient was participating in a trial (Appendix 7) and describing the ethical approvals and safeguards in place. The letter explained that the interventions were adjunctive, and participants advised to continue with any treatments that had been prescribed by their GP; and that interventions shouldn't interfere with pharmaceutical medication.

6.5.1 Treatment by homeopaths

Homeopaths in the trial were all trained, insured and experienced in the treatment of chronic conditions. They were registered with one of the four main bodies representing homeopaths in the UK (Alliance of Registered Homeopaths, Faculty of Homeopathy, Homeopathic Medical Association, or Society of Homeopaths). Initially only homeopaths living in or near Sheffield were included. After 4 months, 3 new homeopaths were recruited from another complementary health clinic (Marlow Homeopathy, in Buckinghamshire) to conduct on-line consultations.

Treatment consisted of an initial consultation of up to 1½ hours between carer, child and homeopath, and up to seven follow up appointments with the same homeopath of 30-40 minutes at approximately 4–6 week intervals. After each consultation, individually tailored homeopathic remedies were prescribed by the homeopath based on information obtained during consultations. Carers were free to contact the practitioner between appointments with queries.

The initial consultation focussed on building up a complete picture of the participant, considering all aspects including diet, medical history, life events, likes and dislikes, lifestyle, behaviour and personality. Prescription of a homeopathic remedy was made by homeopaths matching the composite of symptoms as closely as possible with those of an appropriate remedy. Homeopathic remedies were provided in the homeopath's usual manner: either at the end of the consultation, or sent by post, with instructions about how to take them. Frequency and dosage varied according to the assessment of the homeopath.

At follow up consultations, both carer and child were asked about any changes in symptoms. Depending on this information, the homeopath either continued with or changed the prescription. If carer and child reported improvements there was usually no change in prescription. If no improvements were reported the prescription was usually changed.

6.5.2 Treatment by nutritional therapists

All trial nutritional therapists were registered with the British Association of Nutritional Therapists and were members of the Complementary and Natural Health care Council. At the first consultation of 1 – 1 ½ hours, a health history was taken where nutritional therapists asked about diet preferences, types of food eaten (e.g any ready meals, types of fats, types of drinks, any organic foods, sugar intake), typical daily diet, any food intolerances, lifestyle (sleep, smoking, mercury fillings, medication usage, activity levels), stressors, family history, diagnoses, health concerns, diet related symptoms.

After documenting this information, a summary sheet, supporting handouts, supplement sheets, recipes, and meal ideas were sent to participants. At subsequent consultations of 30-40 minutes, the plan was reviewed and revised, dependent on the family's ability to assimilate and put suggestions into practice.

A range of options tailored to each participant were discussed during consultations. These included: elimination diets such as gluten free and/or casein free; reducing intake of known problematic substances (e.g food colourings, sugar, simple carbohydrates); increasing intake of healthy foods (oily fish, nuts and seeds, protein, fruit and vegetables); substituting less healthy foods with healthier ones; balancing blood sugar; improving drinks/fluids intake, lifestyle advice (sleep, activity, purpose, relaxation, time outdoors); specific dietary interventions for symptoms (particularly gut related); and supplements, which were provided free or discounted by three supplement companies: Igennus, Lamberts and Nutri-Link. These included *Vegepa* (a polyunsaturated fatty acid from Igennus); children's multivitamins, Saccharomyces Boulardii, and Lactobacillus rhamnosus GG probiotic combinations from Nutri-link and Lamberts). Recommended daily intake was 1 capsule each of the probiotics and fatty acids, and 1-3 Multi-vitamin tablets daily depending on age and size.

6.6 Adverse event management

Adverse events were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE, 2010) guidelines and European Commission (2011) guidelines, graded as follows:

- Grade 1: Mild; asymptomatic or mild symptoms. Intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; resulting in significant disability or incapacity.

- Grade 4: Life-threatening consequences; urgent intervention indicated. Subject at risk of death.
- Grade 5: Death related to AE.

All therapists were provided with Adverse Event Assessment Guidelines (Appendix 9) which instructed them to ask about any adverse events experienced in response to treatment at each consultation, and report events of level 3 or more to the PI within 24 hours using an Adverse event form (Appendix 9) and ask participants to contact their GP.

6.7 Risk Management

Therapists were trained to identify and manage children suspected of experiencing any kind of abuse, since ADHD and abuse symptoms can present similarly. They were provided with Risk Guidelines (Appendix 10), based on section 47 of the Children Act 1989 outlined in the Department of Education Safeguarding Policy (2015). This recommends that confidentiality between therapist and family be maintained unless the therapist deems the risk of abuse great enough to require activating statutory safeguarding procedures. Therapists were advised to only breach confidentiality after discussion with the PI, who would then discuss the case with the management committee within 24 hours, and if appropriate, inform the participant's GP with the participant's permission.

6.8 Data collection and analysis methods

6.8.1 Sample size for cohort and trial

It was estimated that 140 participants needed to be recruited to the STAR cohort in order to have outcomes for 30 participants in each arm. 30 in each arm is considered sufficient to estimate the pooled standard deviation of the outcome with a reasonable degree of precision for the full trial (Sim, 2011; Hayman et al 2012).

It was estimated that 20% of children joining the STAR cohort would either not meet trial inclusion criteria or not accept the offer of treatment: 80% of 140 = 112. Attrition of a further 20% was estimated based on the author's preliminary feasibility controlled case series (Fibert, et al., 2016). 80% of 112 = 90.

6.9 Outcome collection and measurement

Outcomes were collected from both carers and from children's school teachers at baseline and 6 months. Carers completed on-line or paper questionnaires (Appendix 2a) in which they named the child's school and suggested a member of staff who knew their child well. Schools were then sent a letter asking this member of staff (or someone else who knew the child well) to complete an enclosed paper questionnaire (Appendix 2b). Carers were re-

minded to return 6-month and one-year questionnaires via 3 x emails and 3 x text messages, after which they were considered non-responders. Teacher outcomes were requested just once by post, addressed to the Head teacher of the school.

6.9.1 Primary Outcome Measure

The primary outcome measure was the ten item Conners' Global Index Rating Scale (CGI), and sub-scores: restless/impulsive (7 items) and emotional lability (3 items) (described in section 3.4.1). Unblinded carer and blinded teacher scores were analysed separately. Raw scores were analysed since ceiling effects occurred with T scores.

6.9.2 Sub-group analyses

Sub-group analyses were performed for those with autism, and those taking/not taking medication. Those with autism were selected since they may respond differently to treatments and have an unmet need for effective treatments (section 2.3.1). Identification of those with co-occurring autism was possible since carers were asked to name all the co-occurring diagnoses their child had received when they completed the CQ.

Analysis was made of those taking or not taking medication for their ADHD to explore whether medication status had any effect on outcomes. When they completed the CQ, carers were asked to name the medications their child was taking, which enabled the identification of their medication status.

6.9.3 Secondary Outcomes

Health related quality of life (CHU 9D) was analysed to potentially enable an economic evaluation alongside the clinical trial. Preference weights were obtained from the creator of the measure (Stevens, 2010) described in section 3.4.5. Responses to individual items at baseline and 6 months were described (Appendix 14).

Five months after the trial started (February 2016) the 18 item Swanson, Nolan and Pelham ADHD index (SNAP IV) was added (described in section 3.4.1). This was advised by the steering committee chair, who recommended measuring specific ADHD symptoms, and because it is free to use compared to Conners questionnaires which have to be purchased.

Teachers, who did not know the allocation status of the children, were asked '*how disruptive has this child had been in the classroom during the last 2 weeks'*; '*how many days off school has this child had in the last 6 months'*; '*has this child been excluded from school during the last 6 months'*; '*does this child has a teaching assistant and if so, for how many hours?*'; and '*does this child receive any other help in school for their ADHD*?' (Appendix 2b).

The carer questionnaire (CQ) asked carers to estimate the number of visits they had had with their child over the last 6 months with doctors, hospitals, social workers, and the police. They were asked whether they had attended or were attending the Family Action or another parenting class, sessions with a psychologist, or homeopathic treatment. They were also asked to describe any other help they accessed for their child, and, on the request of the families piloting the questionnaire, a blank page was left for anything else they wanted to tell us (Appendix 2a).

6.9.4 Cost effectiveness

The cost of treatment by a homeopath and a nutritional therapist over one year was recorded. This included the cost of consultations, venue hire, remedies, supplements, and therapist's wages. Data was collected under guidance from a health economist from ScHARR, and as recommended by NICE (2008). The health related quality of life measure CHU 9D used enables QALY calculation (section 3.4.5). Rudimentary analysis was conducted as a preliminary test of the design and measures.

6.9.5 Statistical methods

Analysis was conducted by the PI. IBM SPSS 21 statistical software was used. All statistical exploratory tests were two-tailed with significance level (alpha) set to 5%. 95% confidence intervals were presented. Each treatment was compared with usual care by creating dummy variables.

Outcomes were measured by carers and (blinded) teachers at baseline and 6 months. Change scores were calculated by subtracting 6 month scores from baseline scores (lower scores indicate better outcomes). This meant positive change scores indicated improvement, and negative change scores indicated worsening. Statistical tests were conducted on the primary outcome (Conner's Global Index Scale short form (CGI) (10 items) and its subscales; and secondary outcome, health related quality of life. SNAP was not analysed since it was introduced 6 months into the trial and insufficient comparisons were available. Descriptive statistics were presented for resource use.

Statistical testing was exploratory since the study was not powered to detect statistical differences. Analysis focussed on confidence interval estimation rather than hypothesis testing. A General Linear Model (GLM) was used. Regression analysis explored the predictive power of the offer of treatment. CGI change score was the dependent variable. Group (the offer of homeopathic treatment or the offer of nutritional therapy, analysed separately) were independent variables. Analyses controlled for the effects of gender (male=0/female=1), ADHD severity (CGI baseline score) and age by including them as covariates.

Intention to Treat analysis

For the primary analyses all participants offered treatment remained within the treatment group regardless of whether or not they took up the offer of treatment. Intention to treat (ITT) analysis is considered the most appropriate analytical approach for pragmatic trials (Campbell, 2007) and is advocated by the CONSORT guidelines for reporting trials (Moher et al., 2010; Zwarenstein et al., 2008).

Numbers and percentages were calculated regarding the acceptability of the offer of treatments. Statistical tests were carried out to identify any systematic characteristics of the age, gender and ADHD severity of those who did and did not accept and receive treatment.

Clinical difference

Standard mean differences (SMDs) (Cohen's d) were calculated to ascertain the clinical effect. The minimal difference to proceed to a full trial was considered to be a SMD of 0.3 (Table 18). The mean treatment change (baseline - 6 months) was subtracted from the mean usual care change, and divided by the pooled variance (collective standard deviation adjusted for sample size). The equation below, for comparison of independent samples, was followed (Lakens, 2013). The effect size calculator provided by Rstats was used (https://www.missouristate.edu/rstats/Tables-and-Calculators.htm). d_s = the standardized mean difference between two groups of independent observations. [1] = intervention group. [2] = control group. *M* = mean change score. *n* = number of participants. *SD* = standard deviation.

$$d_s = \frac{M_1 - M_2}{\sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}}$$

Missing data strategy

To assess whether data was missing completely at random (MCAR) or missing not at random (MNAR) (Rubin, 1976), baseline differences were compared across the three groups, and between those accepting and not accepting the offer of treatment. Post hoc tests were performed if differences were identified. Missing data were imputed using mean substitution for baseline data and Last Observation Carried Forward (LOCF) for 6-month data.

6.10 Feasibility criteria

This pilot RCT assessed the feasibility of the design and interventions. Table 18 summarises the feasibility criteria. Key criteria were the ability to recruit a cohort and to recruit to the

interventions within the stated time frame of two years. This was assessed by measuring recruitment rates and time taken. Numbers recruited in two years were extrapolated to estimate the time needed to recruit to a full trial, and longer than 4 years not considered feasible. The feasibility of recruiting a representative cohort documented ADHD severity, number and type of co-morbidities, medications taken, resource usage, levels of exclusion and criminality, and recruiting from nationally funded ADHD facilities such as special schools, secure units, NHS facilities, and support services. These were presented narratively.

Whether suitable homeopaths and nutritional therapists could be recruited was assessed, with recruitment of two therapists for each intervention considered the minimum required. The uptake and acceptability of treatment measured the number of appointments kept and missed; the taking of homeopathic remedies; the implementation of advice, diets, and the taking of supplements. At least 30% needed to have accessed treatment, and at least 70% of those to have attended at least three consultations.

It was anticipated that there might be high dropout rate and chaotic uptake. The percentage of participants refusing treatment was therefore considered to determine acceptable levels of refusal since too many refusers may lead to high chance of a type II error, and inadequate information to estimate critical parameters for a full trial with reasonable precision.

Adverse events were documented. Any severe adverse events as a result of treatment meant the intervention would not continue to full trial.

The acceptability of the outcome measurements assessed rates of completion by parents and teachers at each time point in the study. Collection methods were adjusted if necessary. Their suitability was assessed by ascertaining whether information could be accurately and usefully collected about ADHD symptoms, health related quality of life, criminality, school exclusion, attendance, extra help, professional resource use, medication and other intervention use, and adjusted as necessary. Whether CGI and SNAP are appropriate and sensitive enough to measure therapist and participant perceived change was assessed with measures to be adjusted accordingly if any systematically missing items are identified. The suitability and appropriateness of statistical analyses to interpret results was also assessed.

Table 18. Feasibility Criteria

Criteria	*Measurement*	*Criteria for continuation to a full trial*	*Discussion*
Recruitment to cohort rates	# recruited in 2 years	% recruited /sample size estimation.	The minimum to proceed to a full-scale trial will consider the number of years needed to recruit the required sample size. Numbers recruited in 2 years will be extrapolated to determine how long a full trial would need to be. The required sample size will be divided by the percentage recruited in 2 years. Duration of the full trial of more than 4 years will not be considered feasible.
Recruitment to treatment rates	% accepting offer	At least 30%.	The percentage of participants refusing treatment will be considered to determine acceptable levels of refusal. Too many treatment refusers may lead to a high chance of a type II error and inadequate information to estimate critical parameters for a full trial with reasonable precision.
Treatment effects (statistical significance)	Standard mean difference (SMD) CGI	Mean = < .3.	Since neither intervention has been tested previously, estimation of the effect size cannot consider previous estimates. Since some preliminary evidence of helpfulness is required, a SMD of 0.3 in those having one or more consultations will be considered sufficient to proceed to full trial.
Treatment effects (clinical significance)	CGI T score	5 percentiles.	A T score change of 5 percentiles is considered clinically significant, since the child has moved from one level of severity to another according to Conners (2005) (see Table 4.4.1).
Attrition: cohort	# PQ's returned at 6 months	At least 30%	
Attrition: consultations	# consultations attended	70% accepting the offer attend 3 consultations.	Therapists will note the number of consultations attended and missed and dropout rates. It is hypothesised that there will be a high dropout rate and chaotic uptake. These statistics will inform the parameters of the full trial. The nutritional therapists will note the acceptability of the different treatments
Acceptability of TQ and CQ	#TQs and CQs completed at baseline and 6 months; # email/telephone/ paper responses	Adjustment of measure, collection methods and trial parameters.	Questions reworded or removed dependent on discussion with carers and teachers, and optimum means of delivering questionnaires explored. An initial scoping exercise suggests that some schools may be reluctant to disclose sensitive information and poor at returning questionnaires.

Adverse events	Clinicians records	No severe adverse events	As defined by the Common Terminology Criteria for Adverse Events (CTCAE, 2010) guidelines and European Commission (2011) guidelines.
Appropriate outcome measurement	# missing items	Adjustment of measure.	
Recruitment of therapists	# recruited fulfilling criteria	At least 2 of each therapy	
Statistical analysis	ANCOVA	Meets assumptions	

Chapter 7 Results of recruitment to the STAR cohort and 1st pilot trial

The aim of this chapter is to describe the results of recruitment to the cohort, and the pilot trial, provide preliminary indications about the acceptability, clinical and cost effectiveness of the two potential interventions for ADHD, and inform sample size calculation for a full trial.

Statistical testing is exploratory. It is suggested that pilot trial analysis should be mainly descriptive because there is likely to be an imbalance in pre-randomisation co-variates, and imprecision in confidence interval estimation (Carfoot, 2002; Lancaster, Dodd, & Williamson, 2004).

Results are considered as thresholds to be reached to see whether sufficient a priori specified differences (identified in Table 18) were seen from the interventions to proceed to the full trial. The statistical analyses are pilot tested to ensure their appropriateness.

7.1 Recruitment to the cohort

144 participants completed the carer questionnaire over a period of 13 months, between September 2015 and September 2016. This was the means by which participants were recruited to the STAR cohort. 19/144 (13%) did not meet cohort inclusion criteria (Figure 2) (Inclusion criteria described in section 6.3.2) or could not be included. 140 completed an online version (www.starsheffield.com) and four completed a paper version. The questionnaire was mostly completed by people describing themselves as mothers, with the exception of an adoptive mother, a legal guardian, an auntie, two foster mothers, a father, and a step mother.

Figure 2. Reasons for exclusion from the STAR cohort

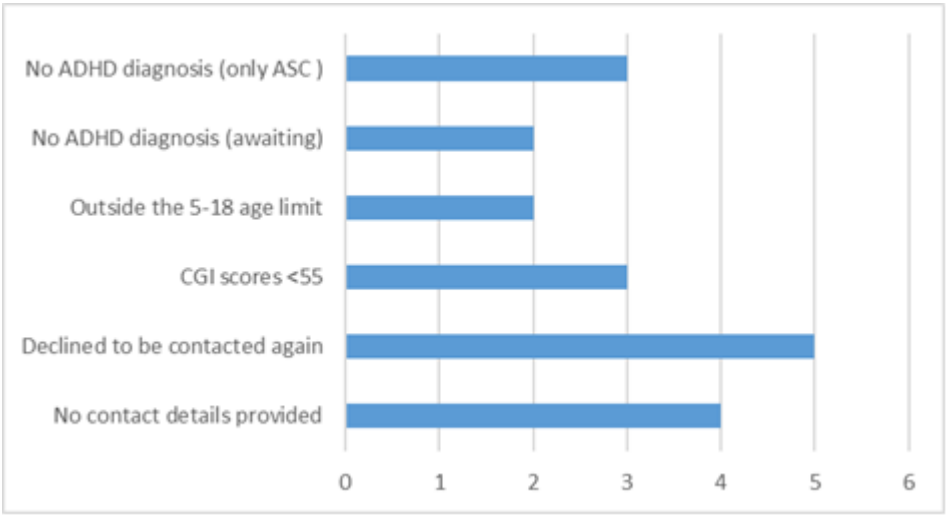
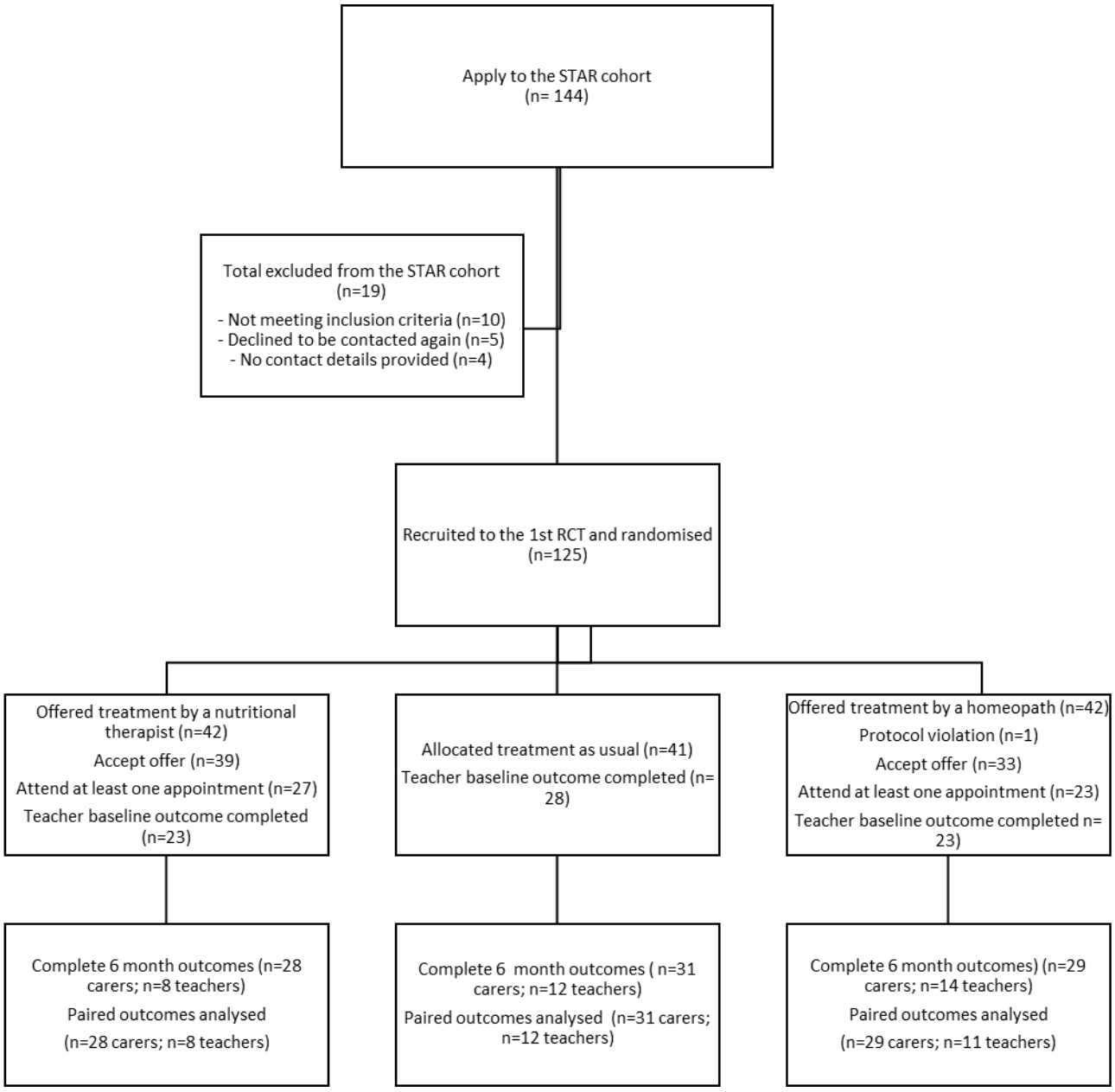


Figure 3. Study progression



7.2 Recruitment to the trial

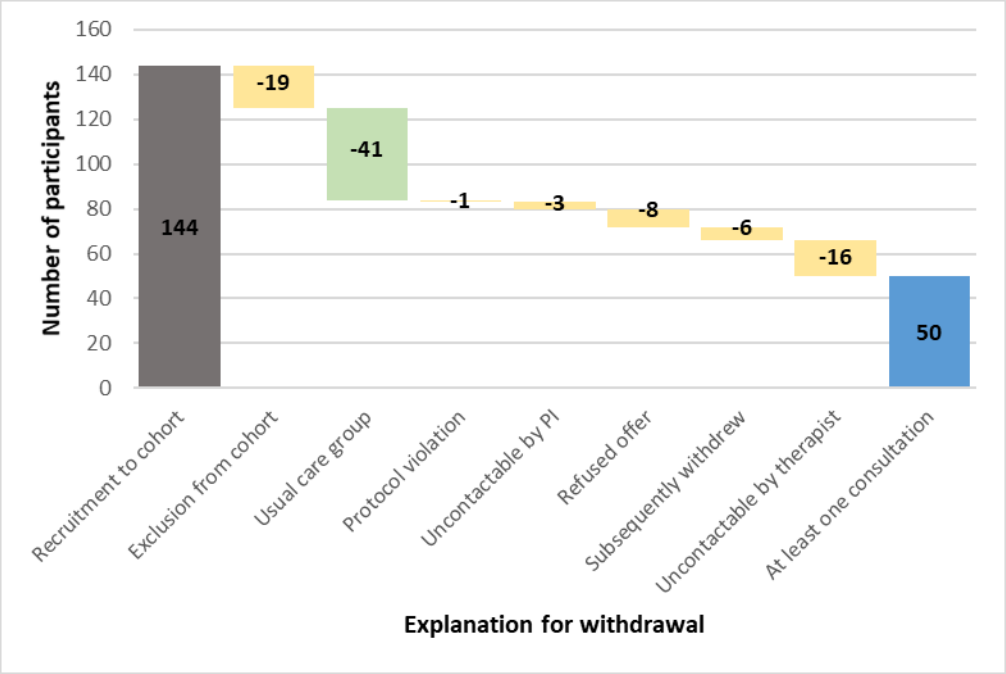
125 cohort participants were eligible for the trial and randomised (stratified according to age, medication status and ADHD severity) to one of three groups. 84 were randomised to be offered a treatment: 42 to treatment by homeopaths (hom), 42 to treatment by nutritional therapists (NT), whilst 41 were randomised to remain in the usual care group (TAU). A total of 20 participants were female, and the mean age was 10.21 (Table 19).

One child randomised to treatment by a homeopath was found to be very sick and awaiting a liver transplant when telephoned to be allocated a therapist. This was in violation of the protocol and he was withdrawn from the trial.

7.3 The offer of treatment

72 of the 83 participants offered a treatment accepted it. 50/72 (n=23 hom; n=27 NT) took up their offer and had at least one consultation. Figure 4 describes the progression from recruitment to the cohort (n=144), through to take up of the offer, describing why n=33 (n=18 hom; n=15 NT) did not take up the offer.

Figure 4. Participant progression from cohort recruitment to first consultation



7.3.1 Trial participant characteristics

The groups were well matched at baseline regarding ADHD severity, age, and medication status due to stratification. Groups were not stratified for gender or co-occurring autism and those with autism were disproportionately distributed, with fewer in the group randomised to the offer of NT than to the offer of hom or to TAU (Table 19).

Those participants who received a treatment were less likely to have autism or be on ADHD medication. Loglinear analysis explored the effect of the disproportionately distributed ADHD medication status in those accessing treatment. The dichotomous variables entered were: group participants belong to (1,2); whether participants take ADHD medications (0,1); and accepting the offer of treatment (0,1). All two and three-way effects were non-

significant regarding the acceptance or not of treatment and medication status (Table 20), although results may not be robust due to small numbers for some combinations. They are included but must be viewed with caution.

Table 19. Baseline demographic and clinical characteristics of study participants according to carers

Outcome	Hom offered	Hom received	NT offered	NT received	TAU	All
	Sample size					
Baseline	N=41	N=23	N=42	N=27	N=41	N=124
	Mean (Standard Deviation)					
Age	10.17 (2.42)	9.78 (2.22)	10.05 (2.46)	10.22 (2.68)	10.41 (2.49)	10.21 (2.44)
Female	8 (19.5%)	5 (21,7%)	7 (16.6%)	4 (14.8%)	5 (12.2%)	20 (16.1%)
Taking pharmaceutical medication	28 (68%)	13 (56.5%)	29 (69%)	20 (74%)	27 (65.9%)	84 (67.7%)
Have autism	13 (10%)	6 (5%)	9 (7%)	6 (5%)	15 (12%)	37 (30%)
CGI T score baseline	88.44 (3.65)	82.40 (5.55)	86.69 (7.52)	76.29 (8.73)	86.9 (6.45)	87.34 (6.1)
CGI raw score baseline	24.0 (3.48)	23.48 (3.27)	23.07 (4.12)	23.4 (3.87)	22.27 (4.62)	23.1 (4.17)
Restless/Impulsive baseline	17.61 (2.63)	17.3 (2.55)	17.4 (3.09)	17.67 (3)	16.98 (3.41)	17.33 (3.05)
Emotional lability baseline	6.39 (1.56)	6.17 (1.59)	5.67 (2.09)	5.74 (1.99)	5.29 (1.93)	5.29 (1.92)

Table 20. Log-linear analysis checking whether medication status affected acceptance of treatment

			Likelihood Ratio		Pearson		
	K	df	Chi-Square	Sig.	Chi-Square	Sig.	Number of Iterations
K-way and Higher Order Effects (Tests that k-way and higher order effects are zero)	1	7	66.528	.000	63.410	.000	0
	2	4	8.179	.085	7.832	.098	2
	3	1	.904	.342	1.022	.312	3
K-way Effects (Tests that k-way effects are zero)	1	3	58.349	.000	55.577	.000	0
	2	3	7.275	.064	6.810	.078	0
	3	1	.904	.342	1.022	.312	0

7.4 Collection of Outcomes

7.4.1 Carer reported outcomes

124 (100%) baseline questionnaires were returned since this was how participants registered to the STAR cohort. 88 (72%) six-month questionnaires were returned. Of those randomised to a treatment, the majority (20/29 hom; 24/28 NT) of returned questionnaires

were returned by those who had that treatment (Table 21). There were no instances of missing data in baseline questionnaires, and five instances of missing data in 6-month CQs completed on paper. Last observation carried forward was used to impute data as stated in the protocol (section 6.9.5).

Table 21. Number of carer questionnaire returns at 6 months

Total number of questionnaires requested	Number returned	*Number NOT returned*	Number returned by those NOT having a treatment	Number returned by those having a treatment
Total: 124	88	37		
Usual Care: 41	31	10	n/a	n/a
Hom: 41	29	12	9	20
NT: 42	28	15	5	23

7.4.2 Teacher reported outcomes

Teacher outcomes were potentially available from a maximum of 100 teachers, since 20 carers refused permission for their child's school to be contacted and 4 children were home schooled (Table 22 shows the distribution according to group). 31 paired questionnaires (baseline and 6 months) were available for analysis (11 (hom), 8 (NT) and 12 (TAU), of which 7/11 (hom) and 4/8 (NT) were from those accessing a treatment (Table 23).

Table 22. Explanation for missing teacher questionnaire returns at baseline according to group

	Permission given to request teacher questionnaire	Carer does not give permission to request teacher questionnaire	Child is home schooled	
homeopathy	30	8	3	41
Nutritional Therapy	37	5	0	42
TAU	33	7	1	41
Total	100	20	4	124

Table 23. Teacher questionnaire returns at baseline and 6 months according to group.

Number of questionnaires requested	Number of base-line re-turns	Number of 6 month returns	Number of paired ques-tionnaire re-turns	Number of paired questionnaire returns by the same teacher	Number of paired questionnaires re-turned for those having a treatment
Total: 100	72	34	31	20	23
Hom: 30	21	14	11	10	7
NT: 37	23	8	8	4	4
Usual Care: 33	28	12	12	6	12

7.4.3 Data cleaning and screening

The SPSS dataset was first cross-checked with the original google sheet and then screened for any missing values and outliers using SPSS descriptive statistics. Where missing values or values outside the correct range were found, values from the original data were checked and correct values input. In 3 instances where age was 0, the correct age was found to be 11. In one instance age had been input as 9.5, and therefore categorised separately, so it was re-input as 9. In two instances the level of disruption (measured using a Likert-type scale from 0-5) was 22 and 33 and should have been 2 and 3. Likewise three SNAP scores of 22 and 21 should have been 2.

Missing values for CGI and SNAP baseline Teacher questionnaires were imputed using mean substitution in accordance with recommendations by tool developers (Conners, p31, 2009): 1 item from CGI3 was missing; 1 item from SNAP8 was missing; 26 items from SNAP9 were missing due to a printing error; and 1 item from SNAP 17 was missing.

7.5 Data analysis

For the primary ITT analysis all paired, returned data was analysed. The per protocol primary analysis (described in section 6.9.5) measured the effect of the offer of a treatment on the 10 item Global ADHD symptom (CGI) change score (and 7 item restlessness/excitability sub-score and 3 item emotional lability sub-score) according to carers and teachers. The analysis compared the offer of adjunctive treatment by a homeopath with usual care, and the offer of adjunctive treatment by a nutritional therapist with usual care. The two treatments were analysed independently.

Two analytic approaches were taken. Multivariate linear regression quantified the impact attributable to intervention and the likelihood that findings were down to chance, controlling for the effects of co-variates ADHD severity (CGI baseline score), age, and gender (being female). The total carer sample size of 88 entered into the regression model whilst considered sufficient to test the overall fit according to Green (1991), is not considered sufficient to test the fit of individual predictors according to Miles & Shevlin, 2001 (in Field, 2005), where suggested minimum sample size is 104 (+ 1 for each predictor), and more if a small/medium effect is expected. The total teacher sample size of 31 was also insufficient. Therefore results must be treated with caution.

Standardised mean difference (SMD) explored the magnitude of the clinical effect (since statistical significance is a function of sample size) and provided estimates for the sample size required in the full trial (see section 6.9.5. for the formula used to calculate SMD). Effect size description considers the rule of thumb presented by Cohen (1992) which suggests that the effect size is small if SMD = 0.2; medium if SMD = 0.5; and large if SMD = 0.8.

Similar analyses were applied to subgroups of interest. The outcomes of those receiving at least one treatment were reported to explore the effect of receiving a treatment (per protocol analysis). The outcomes of the sub-group with co-occurring autism were reported to explore whether there were any differences in outcome between this group and those without cooccurring autism. The outcomes of those taking/ not taking medication were reported to explore whether medication status might impact outcome. These sub-groups were very small and analyses treated with caution.

Secondary outcomes health related quality of life measure CHU 9D were also analysed. The SNAP outcome introduced 6 months into the trial was not analysed due to insufficient data: only 38 carer and 10 teacher paired scores were available, of which there were none for treatment by homeopaths.

7.5.1 The primary outcome

Assumptions

Carer ratings

Data were tested for normality and found to meet the assumptions for conducting parametric tests. Histograms showed the data to be fairly normally distributed, and the normal P-P plot showed points close to the line. Values of skew (.433 (.255)) and kurtosis (1.49 (.506)) were below the significant level of absolute value 1.96. Standardised residuals (min -1.98, max 3.25) and scatterplots showed that the data met assumptions for homogeneity of variance (meaning the variance is similar across groups) and linearity (meaning a linear relationship between the independent and dependent variables).

Multicollinearity (a strong correlation between predictors) was not a concern. Tolerance values ranged from 1 to 1.48. Tolerance values below .10 to 0.25 are considered cause for concern (Tabachnick & Fidell, 1989 & Menard, 1995).

Variance Inflation Factor (VIF) ranged from 1 to 1.36. Bowerman (1990) suggests multicollinearity if VIF values are over 1, although Myers (1990) suggests >10. The Durbin-Watson statistic of 2.14 was sufficient to meet the assumption of independent errors. This statistic varies between 0 and 4, with a value of 2 generally meaning residuals are uncorrelated, although this varies according to the number of predictors (Durbin & Watson, 1951).

Teacher ratings

The data met assumptions for conducting the analyses. Histograms showed the data to be normally distributed, and the normal P-P plot showed points that were not completely on

the line, but close. According to the standard residuals, the data contained no outliers; multicollinearity was not a concern with tolerance ranging from .794 to .944, and VIF of around 1.0. The data met the assumption of independent errors according to Durbin-Watson value which was 1.77, and values of skew (.73) and kurtosis (.32) were also within reasonable limits. The scatterplot of standardised residuals showed that the data met the assumptions of homogeneity of variance and linearity.

Descriptive statistics

Tables 24 & 25 show carer and teacher descriptive data of the primary outcome at baseline and 6 months, according to those offered, and those receiving a treatment. Data show that all groups had reduced scores (which indicates improvement) after 6 months, but that improvement was greater in treatment groups than the usual care group.

The six-month scores of those who accessed a treatment (per-protocol) were not markedly different from those offered a treatment (ITT) because the majority of those who returned questionnaires were accessing treatment. Teacher scores for nutritional therapy found a positive trend in the offer group of n=8, but a negative trend for the n=4 for those who accessed that treatment.

Table 24. Carer descriptive data of the primary outcome at baseline and 6 months according to those offered treatments, receiving treatments, and continuing with their usual care who returned both baseline and 6-month questionnaires

Outcome	**Hom offered**	**Hom received**	**NT offered**	**NT received**	**TAU**	**All**
	Sample size					
Paired outcomes	N=29	N=20	N=28	N=23	N=31	N=88
	Mean (Standard Deviation)					
CGI total Baseline	24.03 (3.57)	23.48 (3.27)	23.07 (4.72)	23.41 (3.88)	22.27 (4.62)	22.91 (4.1)
6 months	20.0 (6.15)	19.65 (5.83)	18.82 (5.59)	18.48 (5.27)	20.06 (5.29)	19.46 (5.4)
Change score	*4.03 (5.76)*	*3.7 (6.26)*	*4.25 (7.69)*	*4.96 (6.58)*	*1.55 (5.89)*	*3.21 (6.49)*
Restless-Impulsive baseline	17.66 (2.87)	17.2 (2.7)	17.18 (3.56)	17.6 (3.09)	16.68 (3.54)	17.16 (3.33)
6-months	15.28 (4.59)	14.9 (4.35)	13.68 (3.89)	13.39 (3.59)	15.19 (3.73)	14.74 (4.1)
Change score	*2.38 (4.55)*	*2.3 (5.1)*	*3.5 (5.23)*	*4.2 (4.2)*	*1.48 (4.52)*	*2.42 (4.78)*
Emotional lability baseline	6.38 (1.47)	6.15 (1.53)	5.89 (2.13)	5.96 (1.96)	4.94 (1.95)	5.72 (1.95)
6-months	4.72 (2.15)	4.75 (2.15)	5.14 (2.09)	5.09 (2.09)	4.87 (2.28)	4.9 (2.16)
Change score	*1.66 (1.95)*	*1.4 (1.79)*	*.75 (3.01)*	*.87 (2.96)*	*.06 (2.08)*	*.81 (2.44)*

Table 25. Teachers descriptive data of the primary outcome at baseline and 6 months according to those offered treatments, receiving treatments, and continuing with their usual care who returned both baseline and 6-month questionnaires

Outcome	Hom offered	Hom received	NT offered	NT received	TAU	All
	Sample size					
Paired outcomes	N=11	N=7	N=8	N=4	N=12	N=31
	Mean (Standard Deviation)					
CGI total Baseline	15.36 (5.43)	15.43 (5.5)	18.12 (4.42)	16.75 (4.35)	10.25 (5.94)	12.45 (5.05)
6 months	14.09 (6.1)	13.86 (8.37)	14.75 (2.82)	19.25 (8.38)	10.75 (5.97)	13.17 (7.37)
Change score	*1.27 (5.73)*	*1.57 (6.45)*	*4.13 (10.23)*	*-2.5 (5.0)*	*.83 (6.98)*	*1.84 (7.43)*
Restless-Impulsive baseline	13.18 (5.1)	13.57 (4.64)	14.75 (2.82)	14.5 (1.92)	10.25 (5.94)	12 (7.28)
6-months	12.09 (6.33)	12.00 (7.28)	10.88 (7.16)	15.50 (4.2)	9.25 (4.83)	10.68 (5.95)
Change score	*1.09 (4.5)*	*1.57 (4.99)*	*3.87 (7.6)*	*-1.0 (4.24)*	*1.0 (6.28)*	*1.77 (6.04)*
Emotional lability baseline	2.18 (1.72)	1.86 (1.86)	3.38 (2.72)	2.25 (2.87)	1.33 (1.37)	2.16 (2.02)
6 months	2. (1.94)	1.86 (2.2)	3.13 (2.64)	3.75 (3.77)	1.5 (1.62)	2.(2.07)
Change score	*.18 (1.47)*	*.00 (1.63)*	*.25 (3.01)*	*-1.5 (1.73)*	*-.167 (1.34)*	*.065 (1.34)*

Primary outcome: ITT analysis

Total score

When CGI total change score was the dependent variable and group (hom or NT), age, gender and ADHD severity the covariates, the model explained a significant amount of the variance in CGI change score (F (5,83) = 4.54, p = .001). This was due to the highly significant influence of ADHD severity (t = 4.225, p <.001) (Table 39; Appendix 13). Neither treatment group, age or gender explained a significant amount of variance.

The influence of ADHD severity on the result may reflect between group differences at baseline since treatment groups according to carers had higher baseline ADHD severity than TAU, but all had similar scores at 6 months (Table 24). However, including ADHD severity in the model reduced the effect due to treatment compared to a simple model, suggesting that this was not the case. It is more likely that regression to the mean occurred, and participant's scores clustered towards the population mean.

Restlessness/Impulsivity

The model explained a statistically significant amount of the variance in the restlessness/Impulsivity CGI subscale (F (5, 82) = 3.53, p=.006), explained by the significant influence of ADHD severity (t = 3.64, p < .000), although treatment by a nutritional therapist also neared statistical significance (t = 1.8, p = .075) (Table 41; Appendix 13). SMD = .418 (Figure 5).

Emotional lability

The model explained a statistically significant amount of the variance in the emotional lability CGI subscale (F (5,82) = 4.89, p= .001), due to the significant influence of ADHD severity (t=4.07, p = < .000) and treatment by a homeopath (t = 2.09, p=.04) (Table 41; Appendix 13). A medium/large effect size (SMD) of .793 was measured for the effect of treatment by a homeopath on emotional lability (Table 26; Table 54 in Appendix 13; Figure 5).

Carer ratings of those accessing treatment (per protocol analysis)

Results were generally similar to those of the offer group. Improvement in restlessness/impulsiveness in those receiving treatment by a nutritional therapist now reached statistical significance (t = 2.11, p= .038) (Table 26; Table 44 in Appendix 13). SMD = .623 (Figure 6).

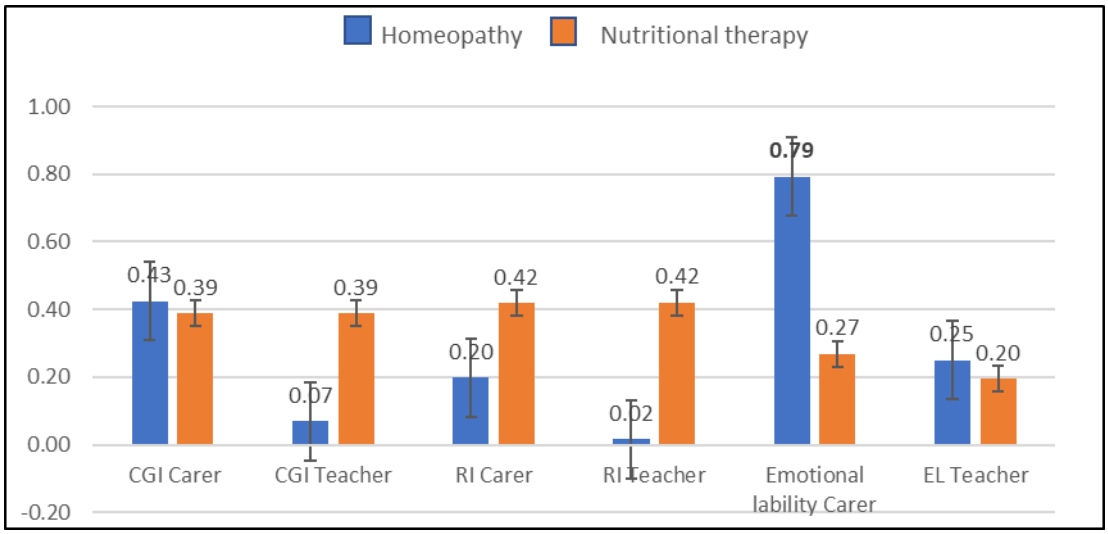
To proceed to full trial, the protocol specified that a CGI total SMD of at least .3 by those having (rather than offered) a treatment was required (see Table 18). This was reached: SMD = .36 hom; and .55 NT (Table 26; Figure 6).

Teacher ratings

Testing may not be valid given the very small number of questionnaire returns, particularly for those accessing treatment (Table 23) (n=7 hom, n=4 NT) meaning results must be viewed with extreme caution. None of the covariates entered into the model explained a significant amount of the variance in teacher-rated CGI total or sub-scores (Table 26; Tables 45,47 & 48 in Appendix 13). There is additional uncertainty in the model due to the completion of outcomes by different teachers (Table 23). The positive direction of improvements due to nutritional therapy in the ITT analysis, and a SMD of .39 (Figure 5), became a negative direction when only those accessing treatment were considered, with a SMD of -.504) (Figure 6).

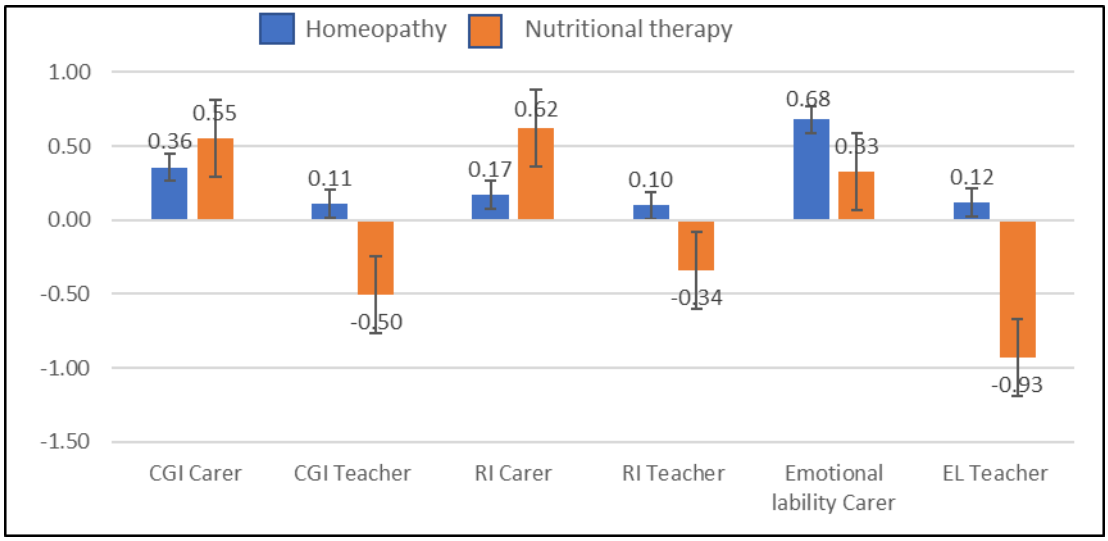
Collection of more paired teacher outcomes is required before any conclusions can be drawn.

Figure 5. ITT analysis of the primary outcome (CGI): carer and teacher-rated effect sizes and confidence intervals



N = 88 carers, N = 31 teachers. CGI: Conners Global Index. RI: restlessness/impulsivity. EL: emotional lability. Effect size calculation = mean treatment change (baseline - 6 months) subtracted from mean usual care change, divided by the pooled variance (collective standard deviation adjusted for sample size).

Figure 6. Carer and teacher-rated effect sizes (with confidence intervals) between 0 & 6 months according to the primary outcome (CGI), in those who received treatment.



N = 74 carers, N = 19 teachers. CGI: Conners Global Index. RI: restlessness/impulsivity. EL: emotional lability. Effect size calculation = mean treatment change (baseline - 6 months) subtracted from mean usual care change, divided by the pooled variance (collective standard deviation adjusted for sample size).

Table 26. ITT and per protocol regression analyses and effect sizes of CGI and CHU 9D, according to carers and teachers

*Total number of observations = 88. Analysis controls for age, gender and ADHD severity. * outcome reached two-tailed statistical significance level <.05.*

Outcome	Completer	ITT / per protocol	R^2	Hom (n = 29 (ITT), n = 20 (received)				NT (n= 28 (ITT), n= 24 received)			
				B[a] (S.E)	t	C.I	Effect size[b]	B (S.E)	t	C.I	Effect size[b]
CGI	Carer	ITT	.215	1.7 (1.57)	1.08, p= .28	-1.48, 4.81	.425**	2.66 (1.55)	1.71, p= .09	-.347, 5.89	.388
		received	.207	1.65 (1.72)	.96, p= .34	-1.84, 5.06	.356	3.05 (1.6)	1.9, p= .062	-.044, 6.44	**.55****
	Teacher	ITT	.290	.58 (2.89)	.2, p= .84	-5.37, 6.53	.069	4.11 (3.14)	1.31, p= .2	-2.35, 10.58	.39
		received	.176	.572 (3.16)	.18, p= .86	-6.09, 7.24	.109	-1.98 (4.15)	-.477, p=.64	-10.74, 6.78	**-.504**
Restless-Impulsive	Carer	ITT	.171	.437 (1.19)	.368, p= .71	-1.9, 2.8	.198	2.13 (1.18)	1.8, p= .075	-.22, 4.47	.418**
		received	.181	.594 (1.3)	.456, p= .65	-2.0, 3.19	.172	2.59 (1.22)	**2.11, p=.038***	.15, 5.03	**.623****
	Teacher	ITT	.264	.176 (2.39)	.074, p= .94	-4.75, 5.1	.016	3.5 (2.6)	1.35, p= .19	-1.86, 8.85	.421**
		Per protocol	.144	.456 (2.74)	.166, p= .87	-5.33, 6.24	.097	-.824 (3.6)	-.229, p= .82	-8.42, 6.78	-.339
Emotional lability	Carer	ITT	.230	1.23 (.59)	**2.09, p=.04***	.06, 2.4	**.793****	.648 (.58)	1.11, p = .27	-.51, 1.81	.269
		Per protocol	.213	1.02 (.64)	1.59, p= .12	-.27, 2.3	**.679****	.612 (.6)	1.01, p= .31	-.59, 1.82	.325
	Teacher	ITT	.251	.403 (.75)	.537, p= .6	-1.14, 1.95	.25	.615 (.82)	.754, p= .46	-1.07, 2.3	.195
		Per protocol	.209	.117 (.737)	.158, p= .88	-1.44, 1.67	.117	-1.16 (.968)	-1.19, p= .25	-3.2, .89	**-.93****
CHU 9D	Carer	ITT	.102	.057 (.031)	1.84, p=.069	-.12, .01	.43**	.084 (.031)	**2.73, p= .008***	-.15, -.023	**1.1****
		Per protocol	.122	.05 (.035)	1.42, p= .16	-.12, .02	.3	.094 (.03)	**2.84, p= .006***	-.16, -.03	**1.19****

*** NICE stipulated minimal clinical important difference < .4 reached. [a] Unstandardised coefficient. [b] Effect size based on Cohen's d.*

7.5.2 Secondary outcomes and sub-group analyses

Autism

37 children had additional diagnoses of autism, of whom paired carer questionnaires were available for just 26 (n=8 hom; n=6 NT, n=12 TAU). Paired teacher questionnaires were available for just 6 (n=1 hom; n=1 NT and n=4 TAU). Due to the paucity of questionnaire returns, only ITT analysis was conducted, and the results of that must be interpreted with extreme caution. A significant effect and a large effect size were seen from those few offered treatment by nutritional therapists (t = 2.88, p = .009, SMD = .92) (Table 54 in Appendix 13).

Medication

Approximately one third of participants did not take ADHD medication, equally distributed across groups due to stratification. No significant differences were seen in groups taking or not taking medication (Tables 51 & 52 in Appendix 13), suggesting medication status did not affect outcome, although samples were very small so no conclusions can be drawn. ADHD severity was the only significant variable, implying that taking medication was associated with ADHD severity.

Health Related Quality of Life CHU 9D

Carers completed CHU 9D, which provided proxy ratings of children's wellbeing. Preference weights were added to the data (section 3.4.5). An overall significant effect of the model was not seen (F (5,82) = 1.865, p= .109) although the impact of treatment by a nutritional therapist was statistically significant (t = 2.73, p = .008) (Table 55 in Appendix 14). Overall, treatment group's health related quality of life improved whilst that of those continuing with their usual care declined (Figure 7 & Table 27).

Table 27. Preference weighted Health Related Quality of Life measure CHU 9D scores at baseline and 6 months for those offered and receiving treatment

	Hom offered	**Hom received**	**NT offered**	**NT received**	**TAU**	**All**
	Sample size					
Paired outcomes	N=29	N=20	N=28	N=23	N=31	N=88
	Mean (Standard Deviation)					
CHU 9D baseline	.679 (.122)	.666 (.121)	.701 (.119)	.704 (.129)	.732 (.090)	.705 (.112)
CHU 9D 6 months	.708 (.137)	.684 (.149)	.759 (.121)	.769 (.116)	.708 (.130)	.724 (.130

Figure 7a. Health-Related Quality of Life CHU 9D utility values at baseline and 6 months

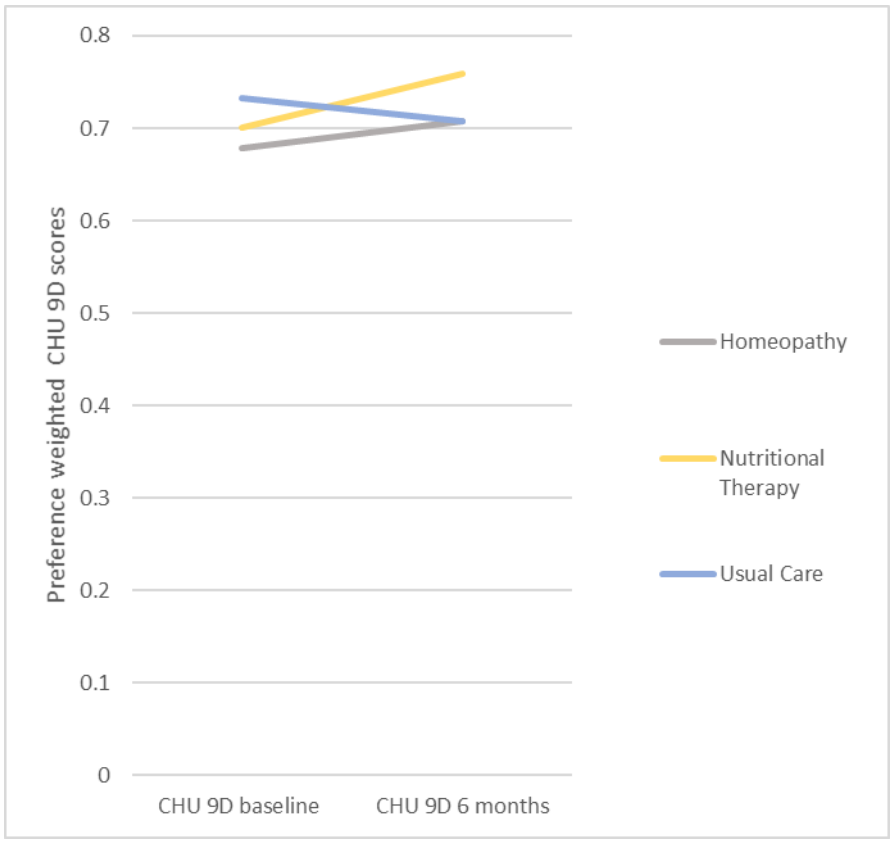
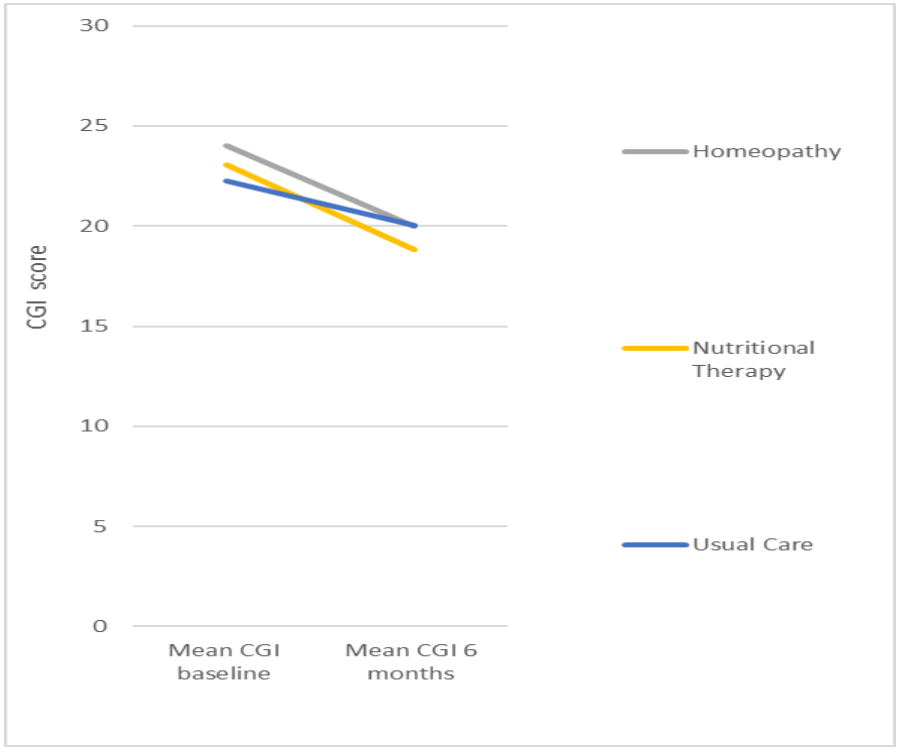


Figure 7b. CGI scores at baseline and 6 months according to carers



The effectiveness of individual items.

Health Relate Quality of Life measure CHU 9D consists of nine items asking about worry, sadness, pain, tiredness, annoyance, schoolwork, sleep, managing daily routines, and joining in. At baseline, carers did not tend to rate their children as being in pain, sad, or tired and registered that schoolwork and management of the daily routine were the most problematic (Figure 21 in Appendix 14).

According to the graphs showing the frequencies of each response (Figure 22 in Appendix 14), carers of those offered treatment by homeopaths observed that their children had reduced concerns with annoyance, sadness, and pain at 6 months compared to baseline, and carers of those offered treatment by nutritional therapists observed that their children had reduced concerns with worry, sadness, and pain. Interventions did not make a difference to schoolwork, management of daily routine, sleep, or ability to join in.

Regression analysis was performed on the sleep item, which asks the level of problems the child had sleeping last night (Table 56 in Appendix 14). No improvements in sleep were found in either treatment group.

7.6 Costs associated with the first STAR pilot trial

The cost of consultations was made up of therapist payments of £55 for the initial consultation and £35 for follow up consultations. Homeopathic remedies were included in this price as is usual in clinical practice. Nutritional supplements were provided free for this trial, however, in private practice it is usual for supplements to be purchased separately. Nutritional therapists reported that they used more supplements than usual because they were free, and because participants struggled to implement dietary advice. Nutritional therapists were asked to calculate the cost of supplementation per 6 months for each of their participants according to their usual practitioner discounted prices.

A travel subsidy of £5 was available for participants, but this was not taken up. Room hire cost an average £10 per session, whilst on-line or telephone consultations incurred occasional postage costs of supplements/remedies averaging £1.50. The table below details the costs currently available.

Table 28. Cost of therapies

	# of appointments	# appointments in consultation room	Supplement costs	Total cost	Mean cost*
First six months					
Homeopathy	91	35	0	£ 3,555	£ 122.59
Nutrition	81	19	7627.94	£ 10,673	£ 368.03
Second six months					
Homeopathy	33	18	0	£ 1,355	£ 46.72
Nutrition	43	5	3794.63	£ 5,370	£ 185.16
Full year					
Homeopathy	124	53	0	£ 4,910	£ 169.31
Nutrition	124	24	11422.57	£ 16,043	£ 553.19

**Mean cost = total cost/number of appointments attended*

7.7 Sample size calculation for a full trial

The target difference considered when determining the sample size is an SMD .4, since this is considered the minimal clinically important difference by NICE, and was also the SMD obtained in the pilot trial.

If significance (alpha error) is 0.05, power 80 %, and effect size 0.4, it is estimated that the responses of approximately 100 participants are required. For power of 90%, responses of 240 participants are needed (Altman, 1991).

Based on pilot study results it is estimated that 40% attrition will occur. Therefore to account for this, for 80% power, randomisation of 166 participants (40% of 166 = 100) is required. And for 90% power randomisation of 400 participants (40% of 400=240) is required.

The results of average 30 participants per group (29 hom; 28 NT, and 31 TAU) are already available from the pilot trial. Therefore randomisation of approximately 136 (80% power)(166 -30 = 136), or 370 (90% power)(400-30=370)) are required.

Assuming equal sample sizes, testing both interventions (i.e 3 arms, but sharing the same control group), this means recruitment of an additional 204 participants to the STAR cohort in total for 80% power (136 + 68); and 555 participants in total for 90% power (370 + 185)

7.7.1 Use of services

Participants provided information about service use at baseline, and at 6 months. No significant change in resource use was found (Table 29).

Table 29. Change in service use between baseline and 6 months

Resource	Hom	NT	TAU	All
Sample size	**29**	**28**	**31**	**88**
Doctor visits (mean) (SD) baseline	1.66 (1.696)	1.14(1.145)	1.55 (1.929)	1.45(1.632)
6 months	1.28 (1.412)	1.04 (1.201)	1.16 (1.508)	1.16 (1.372)
t	***.097 p= .923***	***.657, p= .513***		
Hospital visits total (mean) baseline	1.17 (1.605)	.86(1.008)	1.10 (1.491)	1.05 (1.389)
6-months	.72 (1.066)	.86 (1.008)	.87 (2.141)	.82 (1.505)
t	***.428 , p= .67***	***.763, p = .448***		
Social worker visits total (mean) baseline	.14 (,743)	.25 (.701)	.06 (.25)	.15 (,598)
6-months	.31 (1.137)	.46 (1.374)	.16 (.735)	.31 (1.097)
t	***.284, p = .777***	***.53, p = .597***		
Police visits total (mean) baseline	.03 (.186)	.04 (.189)	.10 (.539)	.06 (.351)
6 months	.07 (.371)	.04 (.189)	.29 (1.616)	.14 (.985)
t	***.811, p = .419***	***.977, p = .331***		

7.8 Summary

Between September 2015 and 2016, 144 participants were recruited to the STAR cohort and 125 randomised to the pilot trial (41 TAU, 41 Hom, 42 NT). Randomised groups did not differ significantly regarding age, gender, or medication use.

72/83 (87%), accepted the offer of treatment. 50/83 (60%) attended at least one appointment. Those who attended at least one appointment were more (but not statistically significantly more) likely to not take conventional medication and have a higher ADHD profile. Non-take up of the offer was greater than estimated, therefore crossover from treatment to usual care was high.

Non-completion of 6-month outcomes was also greater than estimated: 88/124 paired carer questionnaires were returned of which 20/29 hom and 23/28 NT were from those who had treatment. Nevertheless the sample was deemed sufficient to enable sample size calculation for a full trial since paired outcomes were available from 88 participants (29 hom; 28 NT; 31 TAU). Effect sizes of .4 (hom) and .55 (NT) were used to estimate that an additional

454 participants need to be recruited to the cohort in order to have sufficient participants for the full trial of both treatments.

The primary outcome considered carer ratings of the Conners Global ADHD Index (CGI). No statistically significant change due to the offer of treatments was observed according to CGI total score, but statistically significant change was observed the emotional lability sub-score of those offered hom (p= .04, SMD .79). The restless/impulsive sub-score of those who received NT also reached statistical significance (p=.038, SMD = .623). Standardised mean differences for CGI total score was greater than the protocol-specified SMD of .3 for those receiving both treatments: .34 (hom); .55 (NT).

Of a maximum 100 teacher questionnaires, 31 paired questionnaires were returned (11 hom, 8 NT, 12 TAU). No changes were observed in CGI total or sub-scores according to the very small number of teacher scores, which were unstable, with teachers recording a negative effect in the clinical outcome of the n=4 who received treatment by a nutritional therapist (SMD= -.504), but a positive effect (.39) according to the n = 8 teachers of those who were offered treatment. No effect of treatment by homeopaths was found by teachers.

Improvements in health-related quality of life were seen in those offered treatments, particularly of those offered nutritional therapy, whilst reductions in the health-related quality of life of those continuing with their usual care were seen: NT (SMD = 1.1); hom (SMD .43).

Chapter 8 Feasibility results

This chapter assesses the feasibility of the TwiCs design to test the effectiveness of interventions for children with ADHD.

8.1 Feasibility Criteria

The thirteen protocol-specified feasibility criteria and their results are summarised below (Table 30). Some aspects of the TwiCs design did not have a priori stated parameters, and are also considered: the acceptability of the design; the representativeness of the cohort; the effectiveness and acceptability of methods used to recruit participants to the cohort; the acceptability of the interventions; and the acceptability and feasibility of the outcome measures and the collection methods.

Table 30 summarises the protocol-specified feasibility criteria, parameters, results, and whether criteria were reached, with the section referenced where the results are described in full.

8.2 Approvals and governance

The trial received ethical approval from the School of Health and Related Research ethics committee and all subsequent amendments were also approved. University health care research governance procedures classified it as a 'human-interventional study', requiring it to be risk assessed, and considered it low risk.

NHS REC approval was not sought but this decision was challenged. ScHARR Research Ethics Committee (REC) and the University Research and Innovation Services (RIS) confirmed that NHS REC approval was not required.

Table 30. Achievement of protocol specified feasibility criteria parameters

Criteria (Section)	*Measurement: criteria parameters*	*Results*	*Continuation to a full trial yes/no/recommendations*
Recruitment to cohort rates (8.3.1)	# recruited in 2 years: % recruited /sample size estimation	144 recruited in 1 year	Yes
Recruitment to treatment rates (7.3)	% accepting offer: At least 30%	60% (50/83) took up the offer (23 hom; 27 NT)	yes
Treatment effects (statistical significance) (7.5.1)	Standard mean difference (SMD) CGI: mean = < .3 in those implementing a therapy	.36 hom; .55 NT	Yes
Treatment effects (clinical significance) (7.5.1)	CGI T score: 5 percentiles		Use of T scores not feasible due to ceiling effects. SMD (above) used instead
Attrition. Cohort (7.4)	# PQ's returned at 6 months: at least 30%	70% (88/124) six month questionnaires returned	yes
Attrition. Consultations (7.3)	# consultations attended: 70% of participants accepting intervention attend at least 3 consultations	72/83 (87%) accepted the offer. 50(69%) of those had at least 1 consult. 35 (49%) had at least 3 consults.	no
Acceptability of TQ (7.4)	#TQs completed at baseline and 6 months: # of reminders needed; # email/telephone/ paper responses. Adjustment of measure, collection method and trial parameters	54 (43.5%) completed at baseline. 46 (37.1%) completed at 6 months.	Current methods not feasible: more reminders by a variety of methods needed
Acceptability of CQ (7.4)	# reminders needed: adjustment of measure, collection method and trial parameters	Maximum reminders: 3 emails, 1 text, 1 letter.	£10 Boots vouchers introduced improved return rate
Adverse events (8.9)	Clinicians records: no intervention related severe adverse events, As defined by CTCAE (2010) and EC (2011) guidelines.	No severe events	Yes

Appropriate outcome measurement – CQ (7.4)	# missing items: adjustment of measure.	5 items missing from paper questionnaires	Continue using on-line questionnaires
Recruitment of therapists (8.8.1)	# recruited fulfilling criteria: at least 2 for each therapy	8 therapists (hom); 4 therapists (NT)	One (hom) dropped out/unsuitable. Two (hom) using a receptionist & one (NT) only using email made poor contact with participants.
Suitability of consultation venues / mode (8.8.3)	ANCOVA (venue/mode as variable): No venue/mode to have statistically significant impact on treatment effect	This could not be calculated as some therapists used several modes.	
Statistical analysis (7.4.3)	ANCOVA: meets assumptions	Outliers not improved with transformation	Regression analysis used. Assumptions met.

8.3 Recruitment to the cohort and the pilot trial

8.3.1 Recruitment rates

It was estimated that 140 participants needed to be recruited to the STAR cohort, to enable sufficient numbers for the first trial conducted within the cohort, which required at least 30 participants in each of the three arms to have completed treatment (section 6.8.1). Sufficient numbers (n=144) were recruited to the cohort. Half the planned time was required: 24 months was planned, but sufficient numbers were recruited in 13 months.

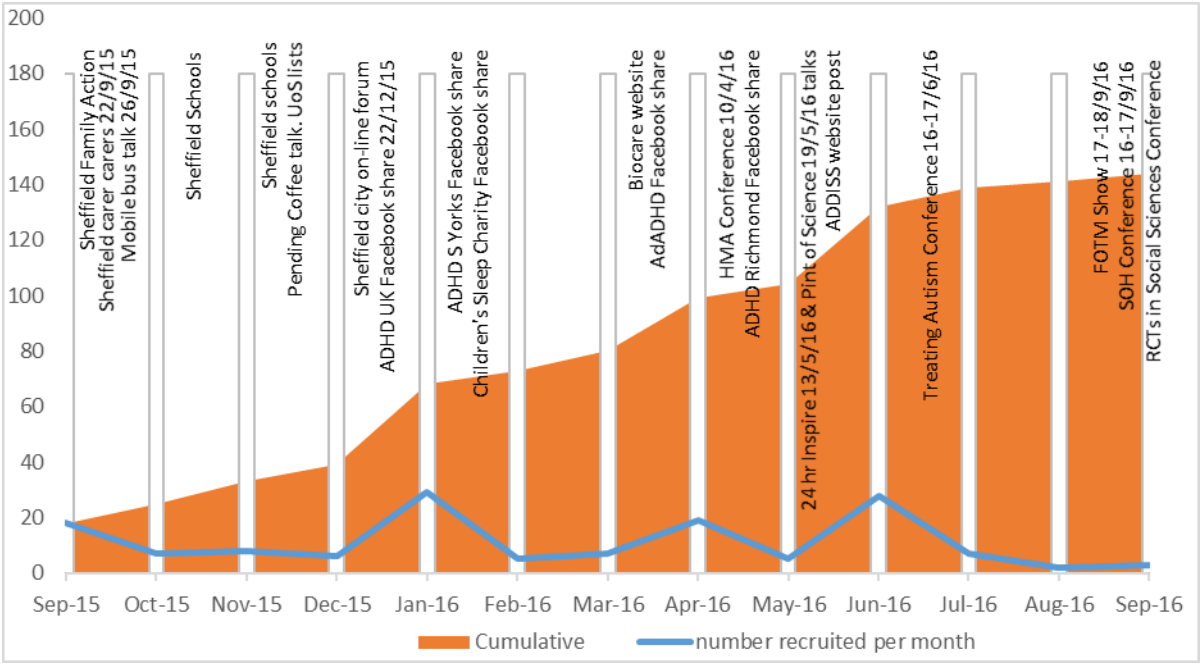
Sample size calculation allowed for 20% of those joining the STAR cohort to not meet trial inclusion criteria or not accept the offer of treatment. 19 would-be participants did not meet cohort inclusion criteria; and 11 participants offered a treatment refused it: 30/144 = 20.8%.

A further 20% attrition was allowed for to enable a final sample size of 90. 88 questionnaires were returned, deemed just sufficient for sample size calculation of ITT participants' outcomes. But insufficient for treatment effect sample size calculation, since not all of those returning outcomes accessed a treatment. Indeed only 50/83 had at least one consultation.

8.3.2 Strategies for recruitment to the cohort

Figure 8 describes the various recruitment strategies employed and numbers recruited, by month.

Figure 8. Recruitment activities and recruitment numbers per month, and cumulatively



Four recruitment peaks (considered to be months when 10+ participants were recruited) coincided with the advertising of the study to: Sheffield Family Action and Sheffield Parent Carers (n=18 September 2015); the Facebook group ADHD UK (n=29 January 2016); the Northampton based ADHD group AdADHD (n=18 April 2016); and the national support group ADDISS (n=28 June 2016).

The most successful means of recruitment were ADHD support groups, especially when enhanced by personal communication with the director. Successful recruitment also occurred as a result of the Festival of the Mind (FOTM) show: the performance video placed on the STAR Facebook page received 10,000 + views, reached 30,000 people, was shared 200 times, and continues to help recruit participants to the cohort (https://www.facebook.com/starsheffieldADHD/videos/677387002419685/).

Recruitment from nationally-funded ADHD facilities such as special schools, secure units, NHS based facilities, and children engaged with support services was not successful. Nor was it possible to recruit from the NIHR-funded Yorkshire and Humber CLAHRC ADHD health tracker cohort. Either NHS ethical approval would have had to be obtained, or there was minimal take up from advertisement, or the process of obtaining the approvals required was too lengthy and onerous. Nor was permission received to recruit from the Newcastle University autism spectrum database (ASD-UK).

Minimal response was received from the 20+ schools contacted. No schools responded to emails, just two schools requested meetings after being visited and no children were recruited from either of those schools. However, 21 participants were recruited from schools with already recruited participants: in 9 instances two children were recruited from the same school, and in one instance, three children were recruited from the same school.

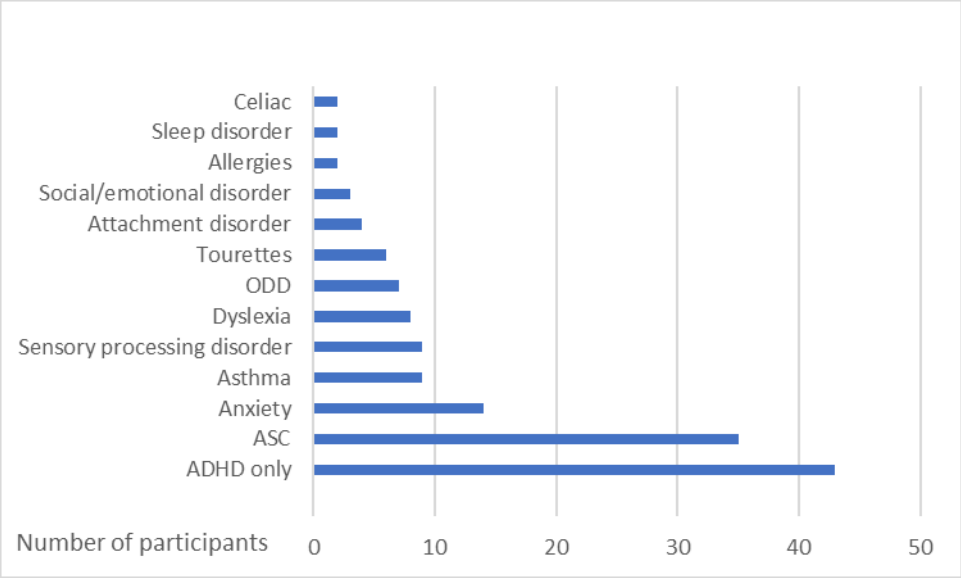
In summary, although recruitment from schools of all types was possible, there was minimal uptake. Recruitment from some nationally funded ADHD facilities was possible, but most required NHS ethical approval. Recruitment from Sheffield city council, CAMHS, and council managed facilities caring for troubled children may be feasible in the future if NHS ethical approval and other permissions are obtained.

8.4 Characteristics of the STAR cohort

This section describes the characteristics of the STAR cohort using data from Carer Questionnaires (CQs) and Teacher Questionnaires (TQs). This data enables an assessment of participant representativeness and what constituted their usual care during the trial. Co-occurring diagnoses, medication use, resources used to support the child, teacher-rated levels of disruption, exclusion, and absenteeism are all summarised.

Co-occurring diagnoses

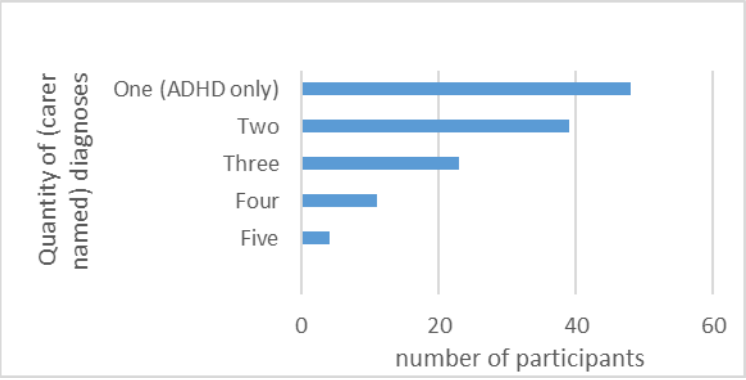
Figure 9. STAR cohort participants' co-occurring diagnoses according to carers



ODD = Oppositional Defiant Disorder. ASC = autism spectrum condition

Of the 125 participants recruited to the STAR cohort who fulfilled cohort inclusion criteria, carers reported that 48/125 (38%) had a sole diagnosis of ADHD (Figure 9), whilst 77/125 (62%) had at least two diagnoses each (Figure 10). The most common co-occurring diagnosis was an autism spectrum condition 35/125 (28%) (Figure 9). The highest number of diagnoses per child was five (named as ADHD, ASC, dyspraxia, a heart condition, high blood pressure, and learning difficulty) (Figure 10).

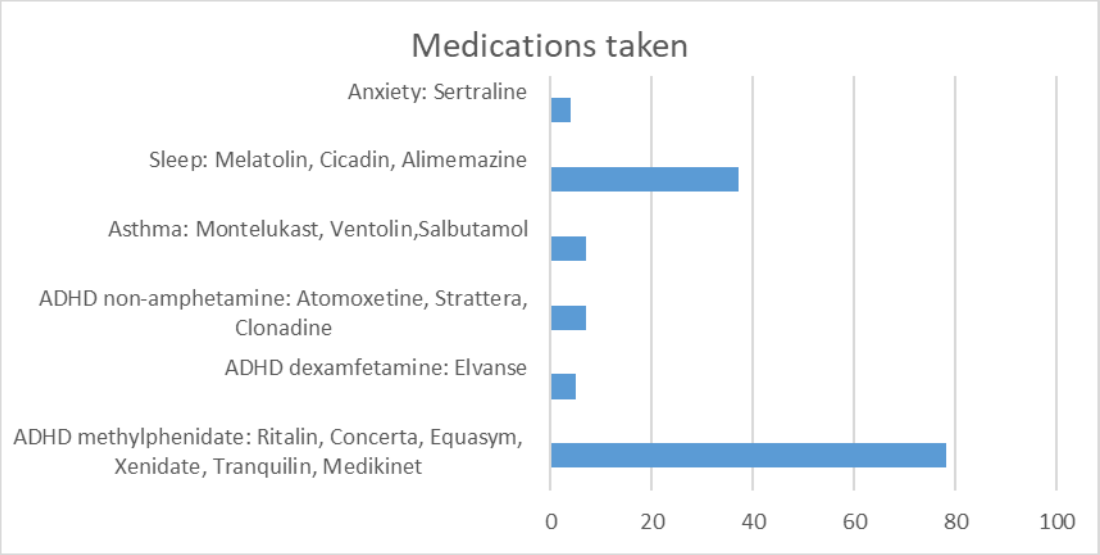
Figure 10. The number of co-occurring diagnoses per STAR cohort participant according to carers



Medication use

Carers reported that 90/125 (72%) of participants were taking ADHD medication (Figure 11) whilst 47/125 (38%) were not.

Figure 11. Medications taken by STAR cohort participants



Supportive resources

Carers were asked about usage of specific services for their children, and these are reported in Table 31. They were also asked to describe any additional help they had used for their child (see Appendix 2a) which is summarised in Table 32.

Carers reported accessing help from a range of sources. They had made many visits to doctors and hospitals: national support services, within school, parenting courses, physical aids, and other therapies - including Complementary and Alternative Medicine (CAM).

Table 31. Services used by STAR cohort participants according to carers

Service	*Total*
Hospital	189 visits (range 1-15)
Doctor	171 visits (range 1-8 per participant)
Social workers	19 visits (by 9 participants)
Psychologist	17 participants (now). 41 participants (in the past)
Police	12 visits (by 5 participants)
Sheffield Family Action Parenting course	5 participants (now). 43 participants (in the past)
Other parenting class	2 participants (now). 69 (in the past)

Table 32. Extra help used by STAR cohort participants according to carers

Category	*Number of families*	*Name (number using)*
Parenting courses	19	123 magic (4); Theraplay (3); triple P, TEACH, positive parenting, change 4 life (1)
Therapies	20	Art therapy, psychotherapy (4); psychology (3); family therapy, play therapy, sensory therapy, occupational therapy, cognitive behavioural therapy, counselling (2); sensory therapy (1)
Physical or visual aids	15	reward charts (7); wobble cushions, fiddle toys, Weighted blankets (2); quiet tent, time out space (1)
CAMHS, Ryegate or MAST	12	ADHD nurse (2); youth worker, MAST worker, gateway worker (1)
Educational	8	SEN support (6), private tutors (2)
Extra-curricular activities	5	trampoline, running club, horse riding, beavers, swimming, theatre school, gymnastics, Pilates, tae kwon do, judo (1).
Complementary and Alternative Medicine therapies (CAM)	22	dietary (11) (fish oils (8), Feingold diet, restricted diet, healthy eating (1); cranial osteopathy, massage (3); homeopathy, hypnotherapy (2), relaxation CDs, crystals, reflexology, reiki, meditation, metamorphic technique (1).

School help

Teachers described providing academic, social, emotional and physical help to children with ADHD. They reported that this help was provided by deputy heads, key workers, classroom teachers, councillors, mentors, occupational therapists, and Special Educational Needs Co-ordinators.

Academic help consisted of part or full-time support in lessons, (particularly for numeracy and literacy), provision of extra time during tests or with homework, personal curricula, and reduced timetables. Several children had learning mentors. Emotional support was provided in the form of mentoring, counselling, involvement with the social intervention team and social skills teaching. Children were part of friendship, nurture and/or social groups. They were provided with a safe haven or extra support at break times, and access to student support.

Teachers described providing behaviour management in the form of visits to the behaviour support team; provision of personal report or break cards; and regular teacher checks regarding distraction. Physical aids used were: disco sit, wobble or ridged cushions; moving

seats; stress balls, twiddlers, fiddle toys; a laptop. Children also received extra sports, occupational therapy, and regular movement breaks. One child had a visual timetable.

School behaviour

On average teachers did not rate the STAR cohort participants as disruptive. According to the 74 Teacher Questionnaires returned at baseline, the mean rating was 2 (SD 1.37) (potential range 0-5). Nor did they have many days off: participants had had an average of 3.34 days off during the last 6 months (SD 6.27). 4/74 (5 ½%) of participants had been excluded for 3.5, 5, 5.5 and 6 days respectively. 34/74 had a Teaching Assistant (TA), ranging from a couple of hours per week, to full time (32+ hours weekly) (n=16).

Carer Issues

The STAR cohort Carer Questionnaire provided an open section for carers to write anything they wanted to. This was completed by 61 participants and is summarised here. Comments are grouped into five emerging categories: friendship, school, home, family circumstances, medication and sleep.

Friendship is an issue for many of the children. Several carers said their child had been bullied, and described their child's struggle with social interaction, lack of friends, that their child is never invited out or wants friends round. Respecting other children's wishes and listening were particular problems. Two carers described how other children actively avoided their children. One child is frightened that children will laugh at him so won't join in with activities. Another child tries hard to be accepted at school and supresses her aggression, which then explodes at home. Some carers said their children did have 'a few good friends', and made friends easily, although in one case also got easily annoyed. One carer said her child's impulsive socialising got in the way of his academic work.

School causes problems for the children and their carers trying to help them participate: '*today he didn't get up until I physically made him, he then missed his bus to school and then had an argument with other students at school during lunch break. When finally I got him organised to sit down and do some homework it turned out he'd lost it on the way home. Quite a typical day!*'. '*He got his first detention today for forgetting his planner'. 'He is unsettled by his new class teacher'. 'A five-minute task can take an hour to complete'. 'Every school trip I have to fight to get him included'. 'Her school work does not reflect her abilities and she is in danger of failing*'. '*He does not remember anything he has done at school and constantly gets into trouble'*.

Home life was described as stressful, particularly in the mornings '*before medication kicks in'*. Children struggle to organise themselves and get ready for school on time. One child was

"*still not dressed today at 5pm despite numerous prompts*", whilst another child was awake and hyperactive from 2am onwards. Routine was important to several children and changes upsetting. One child only wears shorts, needs a particular tightness to his shoes, and '*it is a battle to get him to eat'*.

Relationships within the family were described as challenging: carers described their children as being '*derogatory*' and '*demanding*' at home towards their siblings and carers; carers struggled to manage sibling relationships and '*to get much conversation'*.

Medication received six negative and two positive comments Positive comments were: "*the drug works really, really well. It helps him concentrate on his school work, get along with peers and be more sociably acceptable*"; "*my son's life has significantly improved since starting medication*". Negative comments were: "*he can't take anything for his ADHD due to his blood pressure*"; "*we've stopped ADHD medication as he hates it*"; "*we tried Medikinet, Elvanse, Strattera, Equasym - none have worked – he has terrible reactions to these medications*"; "*we tried Equasim tablets no effect. Now on 36 mg Concerta which was working slightly but since started higher dose he was getting stomach pains and headaches so now reduced back and still same symptoms happen*"; "*Equasym Xl had terrible side effects! Body jerking that was quite violent*"; "*can't take any due to bad reaction on her stomach, tried 5 different ones";* "*we tried Concerta (made him aggressive); Strattera (same as Concerta); Equasym-little effect. Ritalin is having a moderate effect, but his heart rate is reacting to it, so he is only on a small dose*".

Sleep was mentioned by nine carers whose children struggled to get to sleep. Children were described as like a motor that does not switch off even though they are clearly tired. One child had started experiencing night terrors. His carer described him as using the night time as '*a new control time'*. One child is anxious on going to sleep and shouts '*I love you'* every 5 minutes and will get out of bed if he does not get a reply.

Family circumstances. Several carers used the space to describe their child's particular circumstances. Two carers explained that their child was adopted, one expanding that their child '*was removed from birth mum at birth, was in foster care until 17 months old when she was placed with us'*. One child is looked after by his aunt and grandmother (who describe him as being very aggressive towards them) due to his mother's death. Another child '*has had a stressful short life, his father died 2 years ago to a heart attack and he has suffered a lot of bullying, all on top of coping with mild learning difficulties and ADHD. His life is better now. The bullying has stopped, and he has come to terms with the death of his father as much as he can. He is a survivor and I am so proud of him'*.

8.4.1 Summary (cohort representativeness)

For a pragmatic trial, there is a need for the cohort to be broadly representative of those with ADHD diagnoses. This means representation across areas highlighted in chapter 2, such as co-occurring diagnoses, difficulties at school and at home, involvement with the police and/or social services. This section has described the level of co-occurring diagnoses and resources being utilised by STAR cohort participants.

Co-diagnoses are considered to occur in 40-65% of those with ADHD (section 2.1.1). They occurred in 62% of the STAR cohort. The resources being used by participants in the STAR cohort suggest a high level of health needs and use of NHS services: the majority were taking ADHD medication; 67% had made at least one visit to the doctor, and 60% at least one visit to hospital; and one third were also taking sleep medications.

Difficulties at home are suggested by the fact that: 95% of families had accessed or were accessing a parenting class; 46% of families had also visited or were visiting psychologists; and according to the narratives in the free writing section, where just under half the carers in the STAR cohort used the 'anything else you'd like to tell us' section to describe problems with friendships, family life, and school. Difficulties at school are further suggested by the multiple social, emotional and physical as well as educational support being provided by schools. According to the 73/100 teacher questionnaires returned, 56% of children had a teaching assistant, of whom 22% had one full time. 59% of children also received some form of 'other help'. 7% of families were involved with social workers, 5 ½% had been excluded, and 5% had been involved with the police.

8.4.2 Summary (usual care)

Usual care is defined as what participant's carers and teachers said they were currently doing to help the child in their baseline questionnaires. Mainstream healthcare consisted of ADHD medication, which was being used by 72% of the cohort, and sleep medications which were being used by 30%. 5% of families were participating in behaviour change programmes (90% had participated in in the past). 14% were seeing a psychologist. 18% were using some kind of CAM, of which the most popular was dietary, particularly fish oils. 16% were participating in some kind of therapy, such as Art Therapy, (which is currently offered by Sheffield CAMHS), or Play Therapy. 16% reported use of other personnel such as ADHD nurses. 56% had a teaching assistant, of which 22% had one full time.

8.5 The feasibility of randomisation procedures

Stratification according to age and gender was feasible. However, stratifying ADHD severity using CGI T test scores (specified a priori in the protocol) was not sufficiently sensitive, since

n=89 (72%) of participants registered 90+ T scores. Raw scores of 16-23/30 or more are considered '90+' T scores according to the Conners scoring grid.

8.6 The acceptability of the offer of treatment

Figure 12 describes the reasons for refusal of the offer, and Figure 13 describes the reasons for subsequent non-take up of the offer according to each treatment group.

Figure 12. Reasons for refusal of the offer of treatment

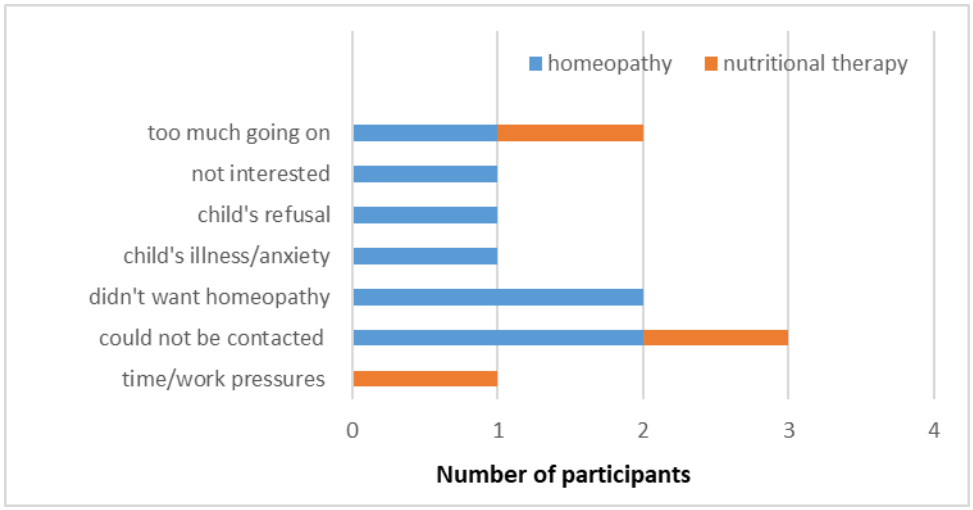
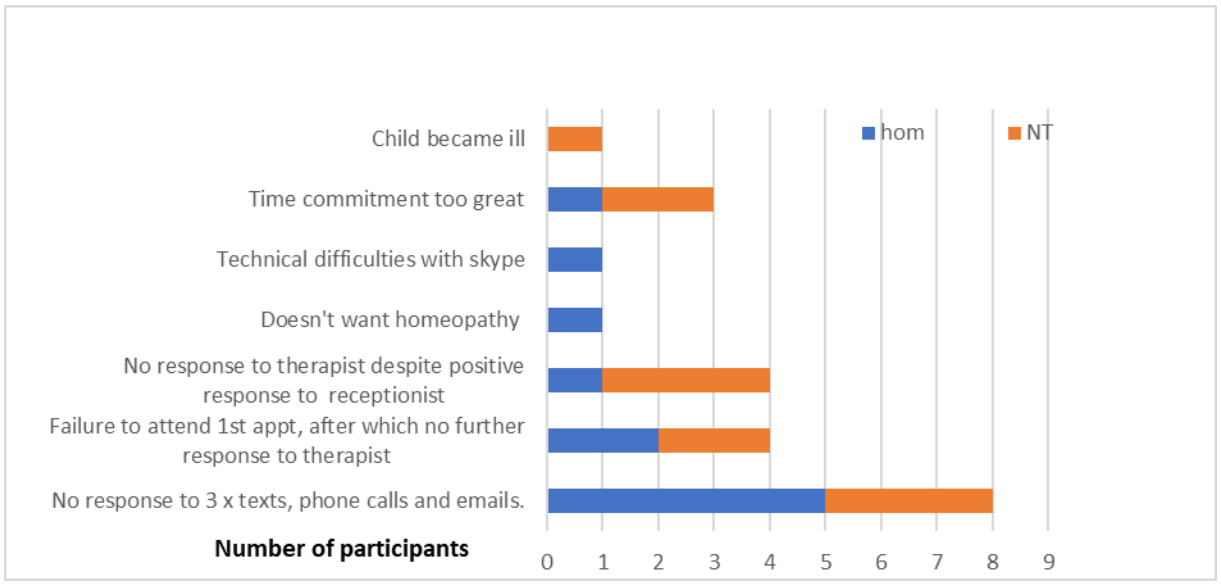


Figure 13. Reasons the offer of treatment was accepted but subsequently not taken up



8.7 Feasibility of outcome collection

144 STAR cohort participants completed baseline Carer Questionnaires (CQs). 124 randomised participants (which included treatment acceptors, non-acceptors and those continuing with their usual care) were requested to complete CQs again six months after completion of their baseline CQ.

An initial request to carers was sent by email, with further emails sent monthly for three months, a text one week after the third email, and a paper questionnaire a week after that. Despite the number of requests, eight months into the trial, return rate of six-month CQs was 17%. After discussion with the steering committee and approval from the ethics committee (amendment number 4, Table 16), an incentive was added. From 28/4/16 onwards, on receipt of CQs, participants were sent a £10 Boots voucher in a card thanking them for being part of the STAR project. Vouchers were also sent to those who had previously returned CQs. This improved the return rate to 72% (section 7.4.1).

A single request, with no reminders, was made for Teacher Questionnaires (TQs) by post. Only one teacher opted to complete the questionnaire on-line. One school replied that they did not want to be involved in the project. 34 six-month outcomes were returned resulting in 31 paired outcomes. Missing cases were excluded list-wise, so only data from participants or teachers providing paired outcomes at baseline and 6 months was analysed. 20 questionnaires (65%) were completed by different teachers each time (section 7.4.2).

Outcome completion: item response

There was very little missing data within the returned CQs and TQs, indicating that outcome completion methods were manageable. Five six-month paper CQs had an item missing (online questionnaires stopped participants moving on until all items were complete). Last observation carried forward was used to impute data in the five instances, as stated in the protocol (Fibert, Relton, Peasgood, & Daley, 2018).

Teacher outcomes were only available from a maximum of 100 teachers, since 20 carers refused permission for their child's school to be contacted and 4 children were being home schooled (see Table 22). There is no explanation for why a further 45 baseline and 53 six-month questionnaires were not returned.

Outcome collection: which measure to use

CGI was purchased from Pearson Assessment company. The free SNAP measure was added at 6 months. Since the majority of baseline questionnaires had already been completed by then, there were minimal paired outcomes for analysis, so the results of the two measures could not be compared. However, SNAP does not provide sub-scores, nor does it measure any aspects of emotional lability since it is now regarded as an associated feature rather

than a cardinal symptom. Since the CGI measures emotional lability, and its sub-scores provided useful information, it was decided to continue with CGI despite the additional cost.

8.8 The acceptability of the interventions

8.8.1 Recruiting homeopaths

In September 2016 five homeopaths were recruited from Sheffield or nearby and saw participants at Wellforce clinic, Sheffield, Western House consulting rooms, Barnsley, or in participants own homes. Homeopaths did not have particular experience with ADHD, however, 3/5 had experience of working with challenging families. All were registered with the Society of Homeopaths.

In January 2017 the study started recruiting participants from across the UK requiring on-line consultations. Since two homeopaths did not want to conduct on-line consultations and three were inexperienced in conducting on-line consultations (no experience, or just one experience), three more homeopaths, experienced in conducting on-line consultations, were recruited from a Complementary Therapies clinic in Marlow, Buckinghamshire, of whom one (myself) had experience of treating children with ADHD, whilst two had experience of working with challenging families.

One homeopath with no experience of working with challenging families, dropped out of the study. Of her five allocated participants: one could not be contacted; one experienced two adverse events (out of a total 7 (section 8.9). Unusually two of her allocated participants contacted me to discontinue treatment; and uniquely, negative mean change scores in the primary outcome (carer) were recorded (see Therapist 1, Figure 17).

8.8.2 Recruiting nutritional therapists

Four nutritional therapists were recruited to the study in September 2016. All therapists had experience working with children with behavioural disorders, and in delivering on-line consultations, so no further therapists were recruited.

8.8.3 Delivery of interventions

This section describes delivery of the interventions according to the checklist developed by Hoffmann et al. (2014) for describing individualised interventions (see section 3.1.7).

Homeopathic treatment

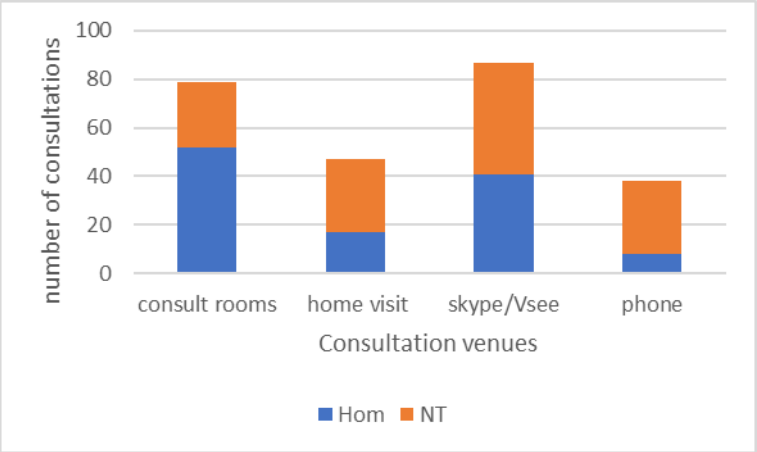
Consultations

Homeopaths offered up to eight regular in-depth consultations to participants over one year, consisting of a first appointment of 1-1/2 hours, and follow ups of 30-40 minutes. Depending on participant locality and convenience, consultations were conducted face to face at complementary health clinics, at participant's homes, on-line using VSee or skype (Figure 14).

Notes were taken by homeopaths during consultations, and afterwards scrutinised for emerging themes, which were then matched with the themes of a homeopathic remedy. The remedy was then delivered to the participant according to homeopaths' usual practice, to be taken in-between consultations.

Homeopaths mostly felt it was important to see the child in person and talk directly to them at each session, either with or without their carer. In one case this led to a participant discontinuing treatment as the carer reported that the child "*didn't like to talk about his feelings*", and several participants found consultations too great a time and emotional commitment. However, others told their homeopaths they valued the experience and appreciated the unusual approach. 4/23 participants opted to continue with private consultations after trial consultations finished. Homeopaths felt that part of their role was being supportive to the children's carers.

Figure 14. Consultation venues used by therapists



Homeopaths reported that carers needed explanations about what to expect from a homeopathic remedy, sometimes found the different approach difficult to grasp, but were often intrigued. They reported that homeopathic remedies were well adhered to.

Those therapists who conducted on-line consultations commented that they liked them, and that they may have improved attendance: "*you can see the child a bit, then talk to mum whilst the child plays*"; "*it helps when they live very chaotic lives*"; "*you can better observe their normal behaviour".*

The therapist who dropped out felt that carers' parenting style contributed to children's bad behaviour, but the majority of therapists expressed great admiration for carers, who they felt "*were up against it*".

Observed difficulties

Homeopaths said that on average, trial participants had more serious symptoms compared with their private clients. They expressed frustration at missed consultations, difficulty contacting participants, and the influence of life events. They felt that their intervention was at times "*a drop in a turbulent ocean*". The therapist who dropped out said that "*treating these children makes me feel incompetent, it's hard not to take missed appointments personally*".

Homeopaths commented that at times they found it difficult to identify a suitable individually-tailored homeopathic remedy. They said that separating the child's story from the carer's story was sometimes difficult since information was delivered by carers, some of whom had traumatic life histories themselves. They found that the symptoms of those children who were on medication were subdued, which was problematic because prescription relies on accurate observation of symptoms. They felt that the child's behaviour was sometimes inhibited in the consultation room.

The interaction between ADHD medication and homeopathic remedies was sometimes a concern for homeopaths, participants and/or their GPs or consultants. Several participants either stopped or didn't start homeopathic treatment on the advice of their doctors. Some participants changed conventional medications during homeopathic treatment which homeopaths reported made analysis of change due to homeopathic remedy difficult. And two participants wanted homeopathic treatment specifically to manage the side effects of conventional medication.

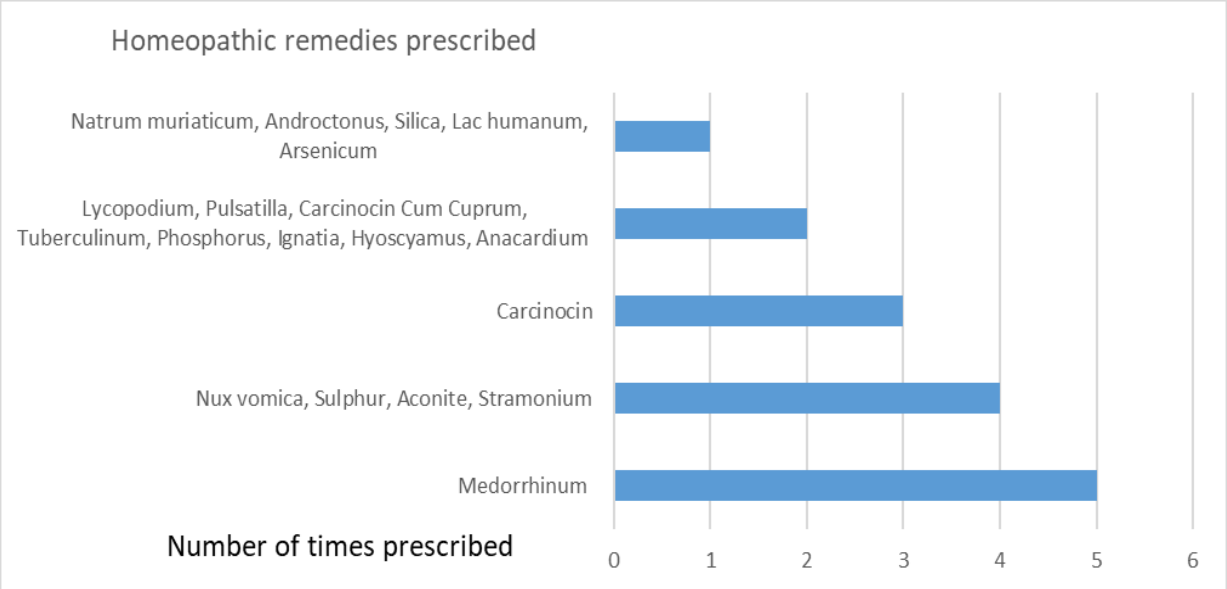
Observed Improvements

Homeopaths reported good improvements with emotional aspects such as anger, meltdowns, anxiety and fear (see 7.5.1 for statistical analysis of emotional aspects). The homeopathic remedies nux vomica, stramonium, pulsatilla and aconite are particularly prescribed for these emotional issues (Vermeulen, 2002)(see Figure 15). Improvements in digestive problems were also reported, particularly in those where the problem was considered a side effect of conventional medication. The homeopathic remedies lycopodium, nux vomica and pulsatilla are particularly prescribed where there are digestive complaints (Vermeulen, 2002). Sleep was also an area which homeopaths felt improved.

Homeopathic Remedies

A total of nineteen different remedies were prescribed by homeopaths (Figure 15).

Figure 15. Homeopathic remedies prescribed to participants



Nutritional Therapy

Consultations

Nutritional therapists provided information about healthy eating, advice on individually-indicated food exclusions, and provided individually indicated supplementation. Like the homeopaths, individual therapists offered up to eight regular consultations to participants over one year, consisting of a first appointment of 1- 1 ½ hours, and follow ups of 30-40 minutes. Nutritional Therapists generally felt that after 5 sessions they had imparted most of their information.

Therapists offered carers the choice about whether to attend with or without their child. Most chose not to attend with their child for the majority of consultations. Unlike the homeopaths, this was not seen as a problem by nutritional therapists, since much of the consultation discussion was with the carer, who was responsible for family meals. In one case the carer didn't want the child to attend as the child didn't know he has a diagnosis of ADHD. Depending on participant locality and convenience, consultations took place at bespoke consultation rooms, participant's homes, by telephone, on-line, or a combination (Figure 14).

Supplementation

Four supplement companies supported the study and provided free supplements: Igennus, Nutrilink, Lamberts, and Biocare. Therapists utilised products from all companies, dependent on product availability, participant sensitivity and therapist preference. Texture and smell sometimes affected participant's ability to take supplements. In routine clinical practice, supplements are paid for by patients in addition to consultation fees, but for this study participants were provided with free supplements. Therapists said they used more supplements than usual, partly because they were freely available, and partly because often participants did not change their bad dietary habits, so supplementation was their main dietary intervention.

Sometimes nutritional therapists had to change the mode, make and texture of the supplements to make them acceptable: some children didn't like capsules, and several wouldn't take fish-smelling oils. Taking a variety of supplements was often found to be overwhelming by participants, so therapists limited prescriptions to a minimum, once daily, to ensure compliance.

Most participants were prescribed polyunsaturated fatty acids. Therapists also provided probiotics and multi-nutrients, and in some cases supplements to aid sleep, anxiety and support neurological issues.

Good eating information.

Therapists reported that best changes were seen where advice was followed. Generally they felt that better results were seen in younger children than teenagers, due to greater carer-control of diets. This was not however, supported by the statistical results, where entering age as a dichotomous variable (primary and secondary age range) had a non-statistical effect on nutritional therapy change score ($t= .127$, $p= .899$).

Suggestions to help children who had extremely restrictive diets, obsessions, or were unwilling to try new foods, were: to work within restricted parameters; change the brand; and/or replace unhealthier with healthier foods, e.g. ham/sausage with chicken/fish.

Therapists said that carers reported being exhausted and overwhelmed which limited their ability to implement new menus. In these cases they only suggested 1-2 recipes at a time, suggested getting the child involved in cooking, and/or focussing on only one mealtime.

Dietary change advice.

Nutritional therapists felt that their advice was variably followed. They reported that those participants advised to and implementing gluten free casein free and/or dairy free diets, saw improvements in soiling, behaviour, general health, and anxiety.

Teenagers tended to have high use of sugar. Therapist's suggestions to manage this were to talk to the teenagers themselves; to suggest they home cook from scratch, e.g. blitz balls; to eat reduced sugar biscuits; to not keep treats at home; and to offer either a pudding or a chocolate bar, but not both. Teenagers also tended to drink fizzy drinks and squash. Therapist's advice to help them reduce their consumption was to start by replacing some of their fizzy drink consumption; to drink water; and to have the occasional sugar free squash sweetened with stevia & sucralose rather than aspartame or saccharin.

To help participants reduce their use of ready meals, processed foods, and wheat and dairy where appropriate, therapists suggested substitutes such as vegan cheese, potato waffles, almond or soy milk, and advised participants to ask their butcher for additive-free meat. Other advice was to always have a (preferably healthy) breakfast, and to increase intake of protein and fibre.

Therapists found that increasing omega 3 intake (e.g. oily fish, nuts, seeds, eggs) was problematic when children were sensitive to tastes and textures. In these cases they suggested hiding seeds in smoothies; having a little at every meal; adding nut seed to cereal; snacking on nuts; putting nut butter on toast; and eating fish twice a week.

Observed difficulties.

Like homeopaths, nutritional therapists expressed frustration at participants who repeatedly missed consultations, and/or didn't follow advice, and commented on the difference between trial participants and their private clients: "*frequent changes to plans (cancellations the day before or 'forgetting' appointments) can be extremely frustrating and obviously happen far more often than with my usual clients, which took some getting used to*". Another therapist said, "*I feel like a supplement pharmacist or I stroke the carers*". Therapists felt that much depended on the carer's attitude: "*if mum has decided it won't work, it does not stand a chance*".

Participants often had poor diets consisting of junk food, sweets, fizzy drinks, and other sugary products. Children, particularly teenagers, bought sweets on the way home from school, which carers could not monitor. Some carers felt unable to implement dietary advice.

Therapists felt that restrictive diets and sensory issues of those with co-occurring ASCs was a problem that often needed working around. They felt that the nutritional intervention was just one cog in a complex wheel with confounding factors which often interfered with treatment. One therapist said "*Sometimes nutrition seems unimportant compared to what I've been hearing about (violent criminal behaviour, trouble with police etc)".*

Observed Improvements

Therapists commented that "*those who put in the effort see the greatest change*". Carers were better able to implement advice when it was kept simple and only one change at a time suggested. They also felt that when families implemented the advice, the health of the whole family improved.

Therapists reported that the best improvements they saw were in children with gastric disturbances, who usually had co-occurring ASCs and supportive carers willing to implement advice. They noted that in some cases carers only acknowledged that change had occurred when supplements were stopped, and behaviour worsened.

When carers were able to implement changes, often all the family did so. Some carers told therapists they appreciated their advice because it validated their parenting, for example carers refusing their children sweets and sugary drinks.

8.8.4 The acceptability of the interventions

How acceptable interventions were was explored by looking at the number of participants accepting the offer of treatment, and the number of consultations attended by participants who had accepted their offer of treatment. Feasibility criteria were at least 70% of those accepting the offer having at least three consultations. This was not reached because although 72/83 participants accepted the offer, only 50/72 (69.4%) then had one consultation. 35/72 (49%) had at least 3 consultations 17/23 (hom); 18/27 (NT) (Figure 16)).

Therapists

Therapists were responsible for contact with their allocated participants once participants had accepted the offer of treatment. Most therapists arranged consultations with participants themselves. Two homeopaths (numbers 7 & 8 in Figure 18), used the clinic receptionist at Marlow Complementary therapies clinic, to contact participants (during working hours), and only managed to contact 33% and 25% of their allocated participants. Two therapists (therapists 4 & 10) were particularly good at contacting and retaining their participants and had the highest average number of consultations. One nutritional therapist (Therapist 11) relied only on email to contact participants, and had few consultations.

Figure 16. Number of appointments attended per participant

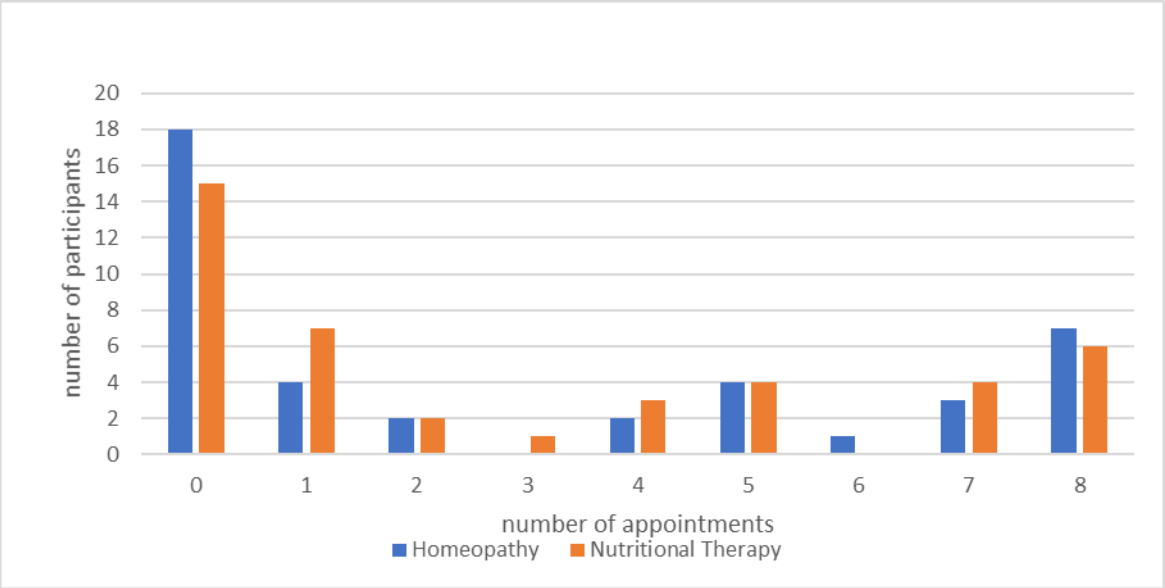


Figure 17. Mean CGI change per therapist

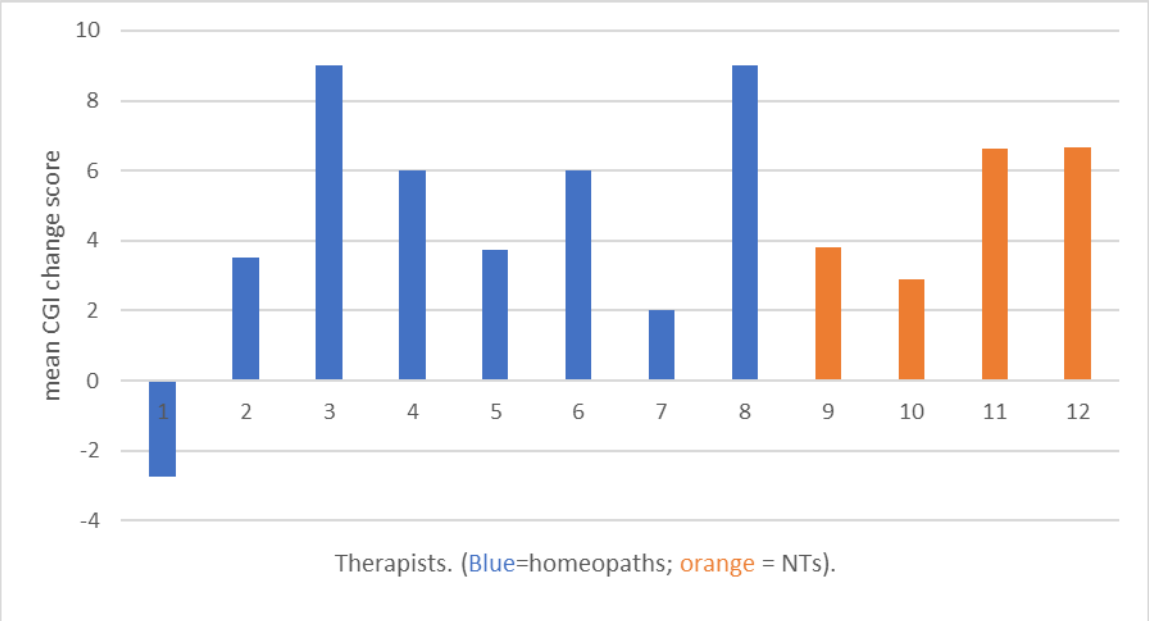
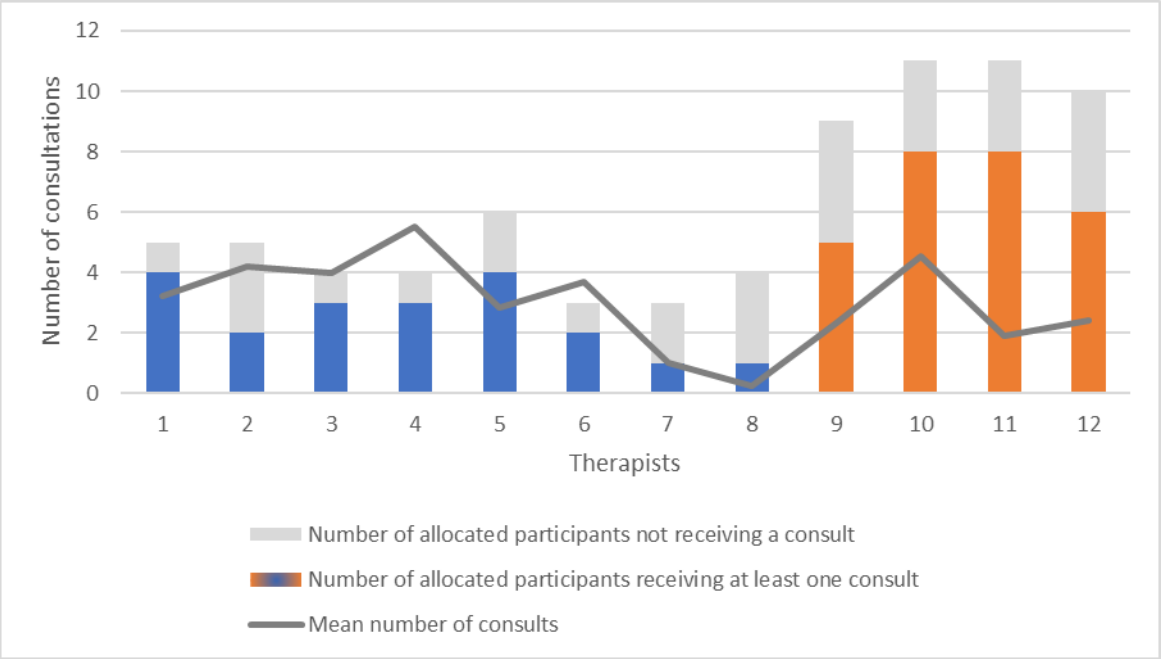


Figure 18. Average number of consultations conducted by therapists, and number of allocated participants receiving consultations



8.9 Adverse Events

Two researchers (PV and PF) independently assessed each reported event to determine the probable causality using the WHO-UMC guidelines, and the severity using the CTCAE guidelines (European Commission, 2011). Where initial assessments did not correspond, cases were discussed, and consensus reached.

A total of seven adverse events were reported by therapists (4 x NT, 3 x hom). The researchers concurred that one of the reports (hom) was not an adverse event, and that two serious, CTCAE Grade 3 events (1 x NT, 1 x hom) resulting in hospitalisation were unlikely to be related to the trial interventions according to WHO criteria. The hospitalisation incidents were: a child with a history of hospitalisation and bad reactions to conventional medications was put on a new conventional medication and subsequently hospitalised; and a child had appendicitis.

Two moderate Grade 2 events (hom/NT) were recorded. One was a worsening of behaviour after provision of supplements; and the other a skin rash considered a probable reaction to a homeopathic remedy (such events are termed homeopathic aggravations).

Three mild Grade 1 adverse events were recorded (NT). Two were considered probable reactions to nutritional supplements (itchy skin, increased aggression) which stopped once the supplements were stopped. One was considered unlikely to be linked to supplements since

stopping them had no effect on the behaviour, and the family considered other life events to have been the trigger.

8.10 Summary

In the previous chapter the statistical analyses, data collection and results were described. This chapter has described the feasibility of the study design and interventions. Nine of the thirteen feasibility criteria were met. Two were not met and two could not be calculated. The suitability of therapist's consultation venues could not be calculated since some therapists used a variety of modes with each participant (section 8.8). Conners T scores could not be used to calculate the clinical outcome since the wide range of scores denoted '70+' meant the measure was not sensitive enough to record any changes (Table 19). Instead SMDs were used.

The single, postal request for TQs did not yield enough responses: TQs were poorly returned both at baseline and 6-months. Furthermore 20/31 Teacher Questionnaires were completed by different teachers each time which reduced consistency and possibly introduced bias. Furthermore, the few paired outcomes returned were unstable (section 7.4). Drop-out from consultations was greater than expected. Although high levels accepted the offer, less than the stipulated 70% then took up the offer and had three consultations. Therefore crossover from treatment to usual care was high.

Recruitment of sufficient numbers to the observational cohort was achieved in half the designated time. A variety of recruitment strategies were used, and recruitment was most successful via social media, ADHD support groups, and Sheffield based Parent Carers, but less successful via schools and publicly funded institutions.

Sufficient participants accepted a treatment, more than the protocol-specified criteria of at least 30%. Carer-rated treatment effects reached criteria for continuation to the full trial (section 7.5.1). CQ return rates were initially very low but they improved with the addition of an incentive. Despite this, return of 6-month outcomes was low from those who had not accepted the offer of a treatment. Nevertheless, the sample was deemed sufficient to enable sample size calculation for a full trial, since paired outcomes were available from 88 participants (29 hom; 28 NT; 31 TAU).

The two serious adverse events which occurred during the trial were unlikely to be related to treatment. However, two of the moderate/mild events reported (NT & hom) were probably due to treatment.

Regarding measurement of outcomes, CGI was suitable to capture the effects of the interventions. The longer (18 item) SNAP measure added at 6 months was considered unsuitable

since it does not measure emotional lability. Measuring emotional lability using the CGI subscale only measures three aspects: mood, temper and tearfulness so finding a broader measure would be useful. It was possible to measure sleep using one item from the CHU 9D, but again, a measure with more items might better measure this important issue. The measurement of hospital, doctor, police and social worker visits, levels of absenteeism, exclusion, disruption, and extra help, all required carers and teachers to recall the previous 6 months, which may not be the most accurate way of obtaining such information since they may forget.

Sufficient therapists were recruited, but one was not suitable for this group of patients. All therapists expressed frustration at the difficulty of making contact, the amount of last-minute cancellations, and non-attendance. Those therapists who contacted participants themselves using a variety of modes were better at making contact than those using a clinic receptionist or single modes.

The sample of participants recruited to the STAR cohort appears to be broadly representative of those with ADHD. The sample reported a range of life-limiting difficulties, high service use within both medical and educational spheres, and multiple services accessed both free at the point of delivery and paid for by carers. The majority of participants had at least two co-morbidities, and several participants were involved with the police or social workers.

Chapter 9 Discussion

This chapter discusses the aims and objectives for the STAR project, for this thesis, and for the pilot feasibility trial. It also considers to what extent the aims and objectives for conducting pilot and feasibility trials in general were achieved. Pilot and feasibility studies are conducted to test the integrity of the study protocol for the future trial; gain estimates for sample size calculation; test data collection questionnaires; test randomisation procedures; estimate rates of recruitment and consent; determine the acceptability of the intervention; and select the most appropriate primary outcome measures (Lancaster, Dodd, & Williamson, 2004).

The long-term aim of the Sheffield Treatments for ADHD Research (STAR) project is to improve outcomes for children with ADHD, by developing a facility for efficiently and objectively testing multiple interventions for them over the long-term. The aim of this thesis is to assess the feasibility of the TwiCs design to provide information to enable the evaluation of treatments for ADHD. The aim of the pilot feasibility study is to assess whether the TwiCs trial design can provide suitable information for stakeholders to enable evaluation of the clinical and cost effectiveness of some treatments for ADHD.

One thesis objective was to describe ADHD, its impact across services, the range and effectiveness of mainstream interventions, gaps in provision, and key issues. This was done in chapter 2, which looked at the evidence base for current mainstream interventions for ADHD, highlighting areas of unmet need, risks of long-term negative outcomes, areas with limited evidence, limitations of current evidence, and challenges in creating the evidence required by stakeholders. Another objective was to identify key stakeholder requirements to assess the acceptability, clinical and cost effectiveness of treatments. This was explored in chapter 3, and the TwiCs methodology was proposed as a potentially efficient and effective way to provide this information to stakeholders.

A range of novel treatments for ADHD being used which have some evidence for their effectiveness were identified. The two selected treatments for ADHD, treatment by homeopaths and treatment by nutritional therapists, were described, and a review of their evidence base conducted in chapters 4 and 5, which was another thesis objective.

Key issues regarding trial designs for these interventions were explored. It was identified that trials to date of both interventions have focussed on the testing of the efficacy of specific elements. Rather than replicating such designs, the decision was made to conduct pragmatic research with pragmatic outputs because explanatory trials do not directly answer the research question as to how effective interventions are to improve outcomes.

Moreover a critique of explanatory designs when applied to complex interventions revealed that they do not in fact measure efficacy as defined in this thesis (section 1.5.4). Nevertheless there will be those who will not consider results from an effectiveness trial valid without prior evidence of the efficacy of specific components, and this may be a limitation of the research.

The STAR project was initiated as a research platform and participants recruited to an observational cohort to achieve the thesis aim. A small-scale test of the methods and procedures – the STAR pilot trial - was conducted, whereby, using a TwiCs approach, the two selected treatments were compared to usual care. The methods by which this was done were described in chapter 6. The results of the STAR pilot trial were described in chapter 7 and the feasibility of the design and interventions were described in chapter 8.

This chapter discusses the thesis objectives outlined above and addresses the remaining thesis objectives, which are to assess the feasibility of a TwiCs approach with regard to: recruiting to time and target a cohort of children with a diagnosis of ADHD; the suitability, acceptability, and deliverability of the outcome measures; the feasibility, acceptability, deliverability, safety, clinical and cost effectiveness of treatment by homeopaths and nutritional therapists for children with ADHD; and the sample size calculation for a full trial.

9.1 The feasibility of the TwiCs design

9.1.1 Recruiting a cohort of children with a diagnosis of ADHD to time and target

Recruiting people to trials in general, and ADHD trials in particular, is difficult. ADHD is disproportionately represented in those for whom life is particularly difficult and such families are unlikely to prioritise involvement in research although they are often desperate for support (Koerting, et al., 2013). Furthermore a feature of ADHD is difficulty in using long-term motivation to inform short-term behaviour, and therefore for families with ADHD, altruism may not be a motivational factor for trial participation which can be acted upon (altruism has been identified as one reason why carers and children (Tromp, Zwaan, & van de Vathorst, 2016), and adolescents (Midgley, Isaacs, & Weitkamp, 2016) may participate in trials). Inefficiency in research is considered an ethical problem (Treweek, 2017).

The TwiCs design is considered well suited to conditions with poor recruitment (Relton, O'Cathain, Nicholl, & Torgerson, 2010) because it requires minimal commitment and no uncertainty. Recruitment to the cohort is more similar to recruitment to longitudinal observational studies than to traditional RCTs (although these can also have recruitment difficulties in ADHD populations (Peasgood, et al., 2016). The TwiCs approach to conducting pragmatic trials is potentially more efficient than standard approaches because embedding trials within existing observational cohorts can facilitate fast and efficient recruitment of participants.

Recruitment to the STAR cohort was successfully achieved in half the predicted time and without use of incentives (section 7.1), and may have been successfully accomplished due to these advantages of the TwiCs design.

Successful recruitment strategies

Whilst it is not possible to definitively assess which recruitment strategies were most successful, the feeling of belonging, personal recommendation, being understood (section 8.3), trying something different, and lack of additional commitment seem to have been motivational. The University of Sheffield is well known and respected by the local population, and the study is called the Sheffield Treatments for ADHD Research. During the first four months recruitment was restricted to Sheffield and environs and 40 participants were recruited. In contrast advertisement on a national ADHD Facebook page with 33,000 members led to just 5 recruits over 3 months, until the study was promoted by an active group member, when there was a sudden upsurge (Figure 8).

Personal recommendations by directors of other websites also led to spikes in recruitment when websites included personal endorsements from them alongside the STAR flyer, but not when flyers posted were unendorsed.

The many responders to the Festival of the Mind video (Appendix 12. Lost Voices) depicting life with ADHD (section 8.3.2) emphasised how much they valued being understood, as expressed in the poem. In the free writing section of the questionnaire carers referred to lack of understanding being a particular issue (section 8.4). Frustration about lack of understanding also dominates posts on an ADHD Facebook page (www.facebook.com/groups/adhduksupport). STAR's strapline is 'making life easier for ADHD'. It is possible that this non-treatment seeking, but 'understanding seeking' population joined the STAR project because they felt allegiance to a project which recognised the difficulties of having ADHD and was committed to 'making life easier'.

Minimal commitment apart from completion of questionnaires, and no delusion regarding interventions may also have influenced recruitment. By comparison another on-going trial of homeopathy using more traditional methods has needed to double their recruitment period. This randomized, double-blind, placebo-controlled clinical trial being conducted in Toronto, Canada has a wait list (usual care) control and a placebo control. It is designed to investigate if there are: a) any specific effects of homeopathic remedies in the treatment of ADHD; b) any specific effects the homeopathic consultation alone in the treatment of ADHD; and c) an overall effect of homeopathic treatment (homeopathic remedies plus consultation) in the treatment of ADHD.

Their estimated recruitment time was based on the results of an open label pilot feasibility study (Brulé, et al., 2014). For the current trial, participants registering interest are informed that they may get placebo interventions, and excluded if they have a diagnosis of an additional mental health disorder including, but not limited to Conduct Disorder, Autism Spectrum Disorder, Bipolar Disorder, and Major Depressive Disorder (https://clinicaltrials.gov/ct2/show/NCT02086864)(Brulé, 2016). The trial started recruiting in 2014 and is still recruiting. The aim is to recruit 177 participants.

A comparison of the two trial designs highlights important differences: STAR used a two stage approach to informed consent, whilst the Toronto trial uses one stage. STAR easily recruits participants to the cohort (the first stage), but less easily retains them at the second stage (the trial). The Toronto study has had less success recruiting participants, since the trial is associated with uncertainty and inclusion criteria are tight. However, the Toronto trial is retaining most of those it has recruited, in contrast to the STAR trial.

Recruitment setting

The STAR project recruited participants in non-treatment seeking settings outside of their NHS based care. Some other studies using the TwiCs design have higher acceptance and take up of the offer of interventions when participants are recruited in the setting where they are diagnosed and attend regularly (Table 34). For example, high acceptance rates were found in studies using the TwiCs design in hospital settings where patients attended for their cancer treatments. However, in a similar setting, (the oncology department of Utrecht University hospital) two trials (Van der Velden and Verkooijen) had contrasting acceptance rates (19% & 90%) suggesting recruitment setting may not be such an influential variable. The amount of effort required by participants to implement the intervention was considered most influential in these two trials (van der Velden, et al., 2017).

Speedy recruitment to the cohort, and take up of a treatment by 60% of those offered it suggests an unmet need by conventional services. The greater uptake of homeopathic treatment by those not on conventional medication also suggests that those participants may have been looking for an alternative.

Recruitment of a representative sample

In the STAR cohort 64% had at least two diagnoses, which is broadly representative of the population (section 2.1). N=7 (6%) had ODD, n=36 had an ASC (29%), n = 8 (6.5%) had been involved with the police, and n=9 (7%) with social workers in the last year (section 8.4), which is less than population estimates (section 2.1). Whilst it was an aim of the STAR pro-

ject to recruit specifically from these groups, where there is most need of effective interventions, the bureaucracy was unmanageable within the time frame.

Therapists reported that participants generally had high levels of need compared to their private patients (section 8.8.3) with several dropping out because they could not manage the extra intervention in chaotic, stressful lives. For example two children (NT) were removed from their home/foster home during the study, and could no longer be involved. One child (hom) was also removed from his mother, but after a short break continued participation with his grandmother.

It was not possible to systematically analyse to what extent the STAR cohort attracted difficult to engage families. This data is important since ADHD is associated with one of the highest dropout rates (Johnson, Mellor, & Brann, 2008), and drop outs have more severe ADHD (Daley & O'Brian, 2013 & Johnson & Jassy, 2007). It has been found that parenting groups tend to be attended by carers with few risk factors, missing those with higher levels of need (Axford, Lehtonen, Kaoukji, Tobin, & Berry, 2012), and that difficult to engage families slip through the net and are service resistant, predicted by low income, single carer status, education/occupation, family size, minority status, severity of child's behaviour, maternal psychopathology and maternal age (Doherty, Stott, & Kinder, 2004). Future collection of data to assess some of these things would be useful but needs to be requested simply and minimally.

The decision was made not to apply for NHS ethical approval to recruit through the NHS (section 6.2) because sufficient numbers of participants were recruited outside of NHS services. Furthermore the process is lengthy and can be difficult to obtain for trials of homeopathy (Viksveen, http://etheses.whiterose.ac.uk/11875/). It is disputable whether this influenced recruitment of a representative sample. One the one hand it may have contributed to recruitment of hard-to reach participants, since those satisfactorily engaged with usual care do not look elsewhere, whilst those joining the STAR cohort may have been motivated by a feeling of unmet need. On the other hand it restricted access to specific target groups of 'at need' children such as the 'looked after' children under the care of Sheffield City council.

The question of whether NHS ethical approval was a pre-requisite for a study of ADHD was resolved (section 8.2), but raised interesting questions and was not a clear-cut decision. The question centred on response to the Medicines Health Authority (MHA) algorithm: *"Will your study involve research participants identified from, or because of their past or present use of services (adult and children's health care within the NHS and adult social care)".* RIS stated that "*the STAR study only recruited children where the carers self-reported that their child has received a diagnosis of ADHD. The diagnosis itself could have come from an NHS service, but it may have come from elsewhere (e.g. a health service in another country) and*

hence the participants have not be identified from, or because of, their use of the NHS specifically". The STAR management team concurred with this. The ADHD population intersects with, and impacts on many publicly funded systems and services, of which health care is only one, such as social care, the criminal justice system and education. However, NHS clinicians maintain that all children with ADHD are under the care of the NHS and therefore NHS ethical approval is required. Furthermore, care within other services tends to include NHS care.

9.1.2 Adherence to the STAR cohort

Although efficient and timely recruitment to the STAR cohort was successfully accomplished, subsequent adherence to that cohort, in terms of completion of questionnaires at 6 months, was less successful. Adherence to treatments and studies is an issue in ADHD research (section 2.3). It is suggested that the disorganization that is a feature of adult ADHD leads to carers being prone to forgetting appointments for their children, and misplacing or forgetting to complete questionnaires (Hay, McStephen, Levy, & Pearsall-Jones, 2001). This issue is likely to be further exacerbated by the six-month stretch between requests for outcomes.

Short-term measurement is likely to achieve better compliance compared to longer term measurement, but long-term measurement is important if long-term outcomes are to be improved. The average length of trials of pharmaceutical medication is 75 days (Storebo, et al., 2015), and evidence suggests that the effects of medication plateau or decrease over time (2.3.1). In comparison, in two small samples, homeopathic treatment improved over time (Fibert, Relton, Heirs, & Bowden, 2016) (von Ammon, et al., 2012), and it is hypothesised that holistic interventions, which attempt to improve the overall health of the individual, may become more effective over time as overall health improves. It is in the interests of stakeholders for these effects to be confirmed or refuted, by measuring the effectiveness of all interventions over the longer term to find long-term, effective interventions. Trials using the TwiCs methodology can do so. The study will also measure 12-month outcomes, although these results are not included in this thesis.

Return of 6-month carer questionnaires (CQs) was initially poor. The return rate was improved by introduction of a £10 voucher (section 7.4), and by asking therapists to remind their participants. Six-month CQs were returned by 88/124 cohort participants. It was estimated that 20% would not return CQs. In reality 29% (36/124) did not return them (Table 21), which meant that paired CQs were available for 88 participants (29 hom; 28 NT; 31 TAU). This was deemed just sufficient to enable sample size calculation.

Of the 83 participants offered a treatment, 44 CQ returns were by those accessing it, and just 14 by those not taking up the offer (section 7.4). So questionnaire return was worst in

those offered a treatment who did not take it up. This suggests that by not accessing a treatment, participants considered that they were no longer part of the STAR cohort. In the usual care group 31/41 CQs were returned, suggesting that they did still consider themselves part of the cohort. This unbalanced questionnaire return occurred in another study using the design (Viksveen, Relton, & Nicholl, 2017). It is of concern because samples may be biased if there are systematic differences between those accessing and not accessing interventions which are not being captured despite use of randomisation and ITT.

9.1.3 The feasibility of recruitment to the 1st STAR trial

The TwiCs design generated fast and efficient recruitment to the STAR cohort and also to the first STAR trial embedded within the STAR cohort. 72/83 participants randomly offered a treatment accepted it. It was estimated (section 6.9) that 20% of children joining the cohort would not meet trial inclusion criteria or not accept the offer of treatment. This estimate was accurate, since 21% (30/144) either did not meet trial inclusion criteria (n=19) or did not accept the offer of treatment (n=11).

The reasons for refusal of the offer of a treatment were time/work pressures, not wanting homeopathy, anxiety/refusal by the child, and no interest (section 7.3). Three participants were uncontactable, despite attempts to contact them by email, phone and letter. It is of course not possible to understand why they did not want to participate. The reasons for non-participation in behavioural interventions (section 2.3.2) concur with some of the reasons given for not wanting to participate in the STAR pilot trial.

9.1.4 Take up of interventions in the STAR pilot trial

Participants allocated to an intervention arm are considered more likely to refuse the intervention using the TwiCs design compared to a traditional RCT design, since those not happy to accept a treatment or a placebo do not consent to join trials, and refuse to participate at the recruitment stage prior to randomisation (van der Velden, 2017). This leads to problems recruiting trial populations: only 33-50% of trials of standard RCTs recruit to time and target (McDonald, et al., 2006 & Sully, Julious, & Nicholl, 2013), and numbers declining to recruit are generally not recorded. However, whilst traditional RCTs may struggle to recruit sufficient participants, they may better retain those they did recruit, as is occurring in the Toronto study described above.

In the STAR pilot trial, attrition and non-participation were shifted downstream (section 7.3). Despite high acceptance (72/83) of the offered interventions, 22/72 did not then take up the offer (Figure 4). This was when the greatest attrition occurred, largely due to therapist's inability to contact them, or due to their not attending a booked 1st appointment and subsequent uncontactability (section 7.3).

It may be that participants did not like to refuse the offer there and then, but having accepted, decided that they did not want to take part and opted out by becoming uncontactable. Or it may be that due to the chaotic and overwhelming nature of participant's lives, initial enthusiasm on a whim could not be sustained. In October 2016, an administrator was brought in to try and contact participants, but was no better at contacting them than therapists.

What is known, is that some therapists were better at contacting and meeting with their participants than others: three therapists (one NT, two hom) had high rates of participation (80%). All were ex-teachers, possibly used to managing communication with parents. In contrast one therapist (NT) only sent emails and contacted just 30%, and two other therapists (hom) relying on a clinic receptionist to contact participants also only recruited 30%. Employing multiple and persistent contact strategies such as emails, texts, and telephone calls at varying times of day had a significant effect on participation. For the full trial, acknowledging this necessity, including those therapists who had high rates of contact and ensuring that other therapists are prepared to be flexible and persistent in contacting participants, may improve take up of the interventions, but may reduce the pragmatism of the trial if therapists usual contact methods are changed. In real-life, therapists employ different strategies and have varying success in contacting and retaining patients.

The higher non-compliance in the experimental arm using TwiCs designs compared with traditional RCTs has so far been found to be influenced by the popularity of the offered interventions (van der Velden, et al., 2017), and the timing of the offer (May, et al., 2017). Table 33 shows the acceptance rates available for trials of a variety of interventions for a variety of conditions using the TwiCs design, with subsequent treatment rates where known.

Table 33. Acceptance rates of trials using the TwiCs design

Research/PI.	*Trial*	*Condition*	*Acceptance of the offer rate*	*Reference*
Lenny Verkooijen	Radiotherapy rectal boost, n=64	Cancer	>90% accept and participate	https://www.TwiCs.global/ethics-symposium-2016
SPIN (Linda Kwakkenbos)	hand exercises (ongoing)	Scleroderma	Approx. 62%	Word of mouth + https://www.TwiCs.global/ethics-symposium-2016
UMBRELLA (Anne May)	Exercise during chemo (n=130)	Breast cancer	55% accept and participate	https://www.TwiCs.global/ethics-symposium-2016
PRESENT (Van der Velden)	stereotactic body radiotherapy, n=53	Cancer, bone metastases,	30% accept, 19% participate	https://www.TwiCs.global/ethics-symposium-2016
DEPSY (Petter Viksveen)	Homeopathic treatment (n=566)	Depression	51.4% accept, 40% participate	Viksveen, 2017.
Clare Relton	Homeopathic treatment (n=48)	Menopausal hot flushes	71% accept and participate	Relton, 2012.
SWELL (Rudolph Uher)	Skills for Wellness, (n=38)	Children at risk of mental illness	83% accept and participate	https://www.TwiCs.global/ethics-symposium-2016
STAR (Philippa Fibert)	Homeopathic treatment or Nutritional Therapy (n=124)	ADHD	87% accept, 60% participate	
REFORM	Podiatry (n=1010)	Older people	87.6% accept and participate	Cochayne, 2017

Information extracted from presentations at the TwiCs symposium (https://www.TwiCs.global/ethics-symposium-2016), the TwiCs website (https://www.TwiCs.global/) and subsequent communication with study PIs.

9.1.5 The acceptability of the STAR pilot trial interventions

For the interventions to be feasible, it was deemed that at least 70% of those *accepting* the offer should have at least three consultations since this is what therapists typically recommend to their new patients. Although there were high levels of acceptance, there were low levels of take up: 72/83 participants accepted the offer, 50/72 (69.4%) had at least one consultation, and 35/72 (49%) at least 3 consultations.

70% (35/50) of those *taking up* the offer had at least three consultations, which may be a better assessment of the acceptability of the interventions. When designing the trial, it was erroneously assumed that those accepting the offer would then start treatment. Therapist's contacting strategy rather than intervention's acceptability was probably a more influential factor on poor take up than the acceptability of the interventions. Greater refusal of the offer is to be expected (van der Velden, 2017) and needs better factoring into the trial design.

Despite attrition, lack of uptake and poor outcome return, levels of uptake and outcome measurement in the STAR pilot trial compared favourably with ADHD trials of non-pharmaceutical interventions. Results for behavioural interventions were presented in section 2.3.2., where they were found to vary widely (Daley & O'Brian, 2013; Thompson, et al., 2009; Taylor, et al., 2015; Barkley, et al., 2000). These, and results for other non-pharmaceutical interventions similar to those tested were summarised in Table 34.

ADHD trials of individualised, CAM, course attending, and/or therapist administered interventions were identified by searching Web of Science, Google Scholar, Clinical Trials.gov, and the International Standard Randomised Controlled Trials Registry (ISRCTR) for pairs of protocols and results of RCTs of non-pharmaceutical interventions between 2006 and 2016. The search terms RCT + ADHD + neurofeedback/acupuncture/parenting/behavioural/non-pharmaceutical were used. Hand searches for the protocols of studies were also made. Nine studies were found where study protocols and study results could be compared for planned and actual recruitment numbers.

Table 34. Recruitment and retention rates. Comparing the STAR trial with trials of comparable interventions

Trial author, publication date. Venue	*Interventions*	*Planned sample size*	*Actual no: randomised*	*Drop out no: %*	*Reasons given for drop out.*	*Final data analysis no:*	*Recruitment period*
Gelade (2016).Holland	NF v meds v exercise	186	112	9 (8%)	Motivational, practical, medical contraindications	102	4 years
Duric (2012). Norway	NF v meds	285	130	39 (30%)	Didn't start treatment (carers' decision,30; subject's decision, 6); didn't complete follow up questionnaires (3)	91	3 years
Thompson, (2009). UK	NFPP v TAU	77 screened	41	11 (27%)	no assessments, more severe ADHD	30	18 months
Daley (2013). UK	NFPP-SH v wait list	?	43	7 (16%)	Lost to follow up	36	?
Sayal (2016). UK	TAU v 123 magic: carer v carer+teacher	288	199	107(54%)	Interested but didn't attend (19). Not interested/ not contactable (88)	76	?
Sprich (2016). USA	CBT v wait list	50	46	3 (7%)	No longer living nearby (1); lost to follow up (3)	36	2 ½ years
Boyer (2015). Holland	CBT-PML v CBT-SFT	?	159	31 (19%)	No interest (6); suicidal ideation (1); acute family crisis (1); lost to follow up (15)	136	?
Axford (2012). UK.	IY v wait list	144	110	53 (48%)	Lost to follow up	57	1 year
Hong (2016). Korea	Acupuncture v TAU	80	93	32 (34%)	Fearful (2). Refused to participate (26). Took additional ADHD medications during the study (4).	61	2 years
Fibert, 2018. UK	Treatment by homeopaths & Treatment by nutritional therapists v TAU	112	124	35 (28%)	time/work pressures (2); could not be contacted (11); did not want homeopathy (3); child's illness/anxiety (2); child's refusal (1); not interested (1); too much going on (5); Lost to follow up (10)	89	13 months

NF= neurofeedback. Meds = stimulant medication. NFPP= New Forest Parenting Programme. NFPP-SH = New Forest Parenting Programme Self Help. IY= Incredible Years. TAU= Treatment as Usual. PML= Plan My Life. SFT= solution focused therapy

Two studies, of acupuncture by Hong (2016) and CBT by Sprich (2016) recruited close to their planned sample sizes, but the required numbers were less, and more recruitment time allowed, compared to the STAR trial. The remainder of studies failed to recruit their planned sample.

Information about acceptability is not routinely collected using traditional designs, but is captured when using the TwiCs design. The levels of drop out described in Table 34 are likely to reflect the degree of pragmatism of the trial. Information across trials with similar degrees of pragmatism would be useful to ADHD stakeholders wanting to make decisions about ADHD interventions and improve negative outcomes, because the population is considered difficult to engage with (Koerting, et al., 2013). There is little point in having efficacious or effective interventions if they are not acceptable to their population.

9.1.6 Compliance with interventions

Compliance with interventions is considered one of the most important outcomes of pragmatic trials (Godwin, et al., 2003). Poor adherence to interventions by those with ADHD has been identified as a problem (section 2.3.2). For the STAR pilot trial, 8 sessions, or one year's treatment, were potentially available to participants, which is more than is commonly accessed in private care. N=50 (60%) had at least one consultation, n=69 (43%) had at least three consultations, and n=16 (19%) had all 8 sessions (section 7.3 & Figure 16). The mean number of appointments accessed was 3, which is interesting since this is what therapists in private practice recommend to establish treatment (section 4.2.5). Nutritional therapists felt that they had delivered the majority of their information after 5 sessions.

Therapists tended to reduce the frequency of consultations once they felt progress was being made, and participants then contacted therapists for renewal of their prescriptions. Participants who attended all available consultations tended to be carers of fostered or adopted children. For the full trial, the offer of a maximum of 5 sessions over one year might be more cost effective.

Research to manage compliance issues recommends: clear recruitment processes; good communication and liaison with stakeholders; incentives for recruitment and retention; active and creative outreach work; investment in building relationships with carers; making programmes easily accessible; having realistic expectations (Axford, Lehtonen, Kaoukji, Tobin, & Berry, 2012); collaboration with teachers; individually tailored, flexible interventions incorporating additional contact in-between sessions if required; a positive therapeutic relationship; and good inter-agency collaboration (Koerting, et al., 2013). Koerting identified 28 barriers to participation which are listed below in Table 33 with their relevance to the STAR study and some possible solutions.

Table 35. Barriers to, and facilitators of, participation by ADHD families identified by researchers, and their relationship to the STAR project

Barriers	*Relevance to the STAR study*	*Possible improvements*
Situational barriers Practical difficulties (transport; childcare; financial difficulties; location; inconvenient timings; unpleasant venue; parking)	Yes, especially initially where participants were required to attend face to face. Most therapists were flexible about time and venue	On-line consultations (implemented) Paying for travel (implemented)
Time constraints due to other commitments (work; issues associated with having several children)	Yes, cited by most carers who dropped out/ failed to attend/didn't accept offer	Extreme flexibility: offer times to suit individuals, flexibility about attendance of the child; keep persisting.
Psychological barriers Fears/Worries (lack of confidence; shyness; concern about being judged; concern about not having skills)	Yes, fear/worry about explaining to therapists about missed appointment, or inability to implement intervention (particularly NT)	Understanding by therapists. Regular supervision to help therapists not take cancellations personally
Stigma (shame about needing help; service use perceived as parental failure; fear of being labelled)	n/a	
Distrust (concern about lack of confidentiality/anonymity; distrust of professionals)	Confidentially/anonymity emphasised throughout Therapists may be seen as professionals and distrusted	Emphasise the non- conventionality of treatments?
Lack of information/misconception about services	Initial enthusiasm to recruit to the cohort and trial not followed up by attending a consultation	More information about treatment commitment on recruitment to the cohort
Availability of services	n/a	
Poor interagency collaboration	STAR project not accepted by NHS clinicians	Apply for NHS ethical approval
Dislike of group activities	n/a	
Programme regarded as unhelpful	Changes may be slow to manifest	Therapists provide realistic explanations
Difficulty following the programme	NT ask carers to implement difficult dietary changes	NTs suggest small changes over time.
Change in circumstances (illness of any family member; move to a different area	Yes, several carers cited this as the reason for dropping out	Flexibility in the programme to drop in and out according to circumstances

Facilitators	*Relevance to the STAR study*	*Possible improvements*
Effective advertisement/service promotion	Yes, multiple sources used, and personal communication	
Effective advertisement content (clear, easy to understand—regardless of literacy levels; conveyance of tangible benefits of programme and inclusive nature of services)	Yes, although conveyance of tangible benefits of interventions may have been downplayed in order not to contaminate research and introduce bias.	Up-play tangible benefits?
Specifically target hard to reach groups	Yes: Sheffield City council looked after children programme, special schools. Criminal justice system. Lack of NHS ethics precluded use of this source	NHS ethics would have allowed access to Sheffield City Council programmes. Target correction facilities.
Offer multiple, 'soft' entry points	Yes	
Personalised recruitment	Yes	
Effective, direct channels (other carers/word of mouth; outreach work; emails; phone calls; text message	Yes	
Good interagency collaboration	No, interventions currently seen as alternative and not promoted/supported by mainstream services	Continue to develop relationships with service providers.
Programme addresses families' actual needs	Yes, programmes are individually tailored to family's needs. Participants without gut problems or where nutrition is not an issue may find NT irrelevant.	Work towards sub-group randomisation, e.g. NT for those with identified gut issues.
Positive group experience (homogenous groups; establishment of ground rules [e.g. confidentiality, safety]; provision of food)	Homeopaths fails to make tangible, immediate differences	Homeopaths to provide clearer expectations of treatment progression
Additional contact (home visits or one-to-one support; phone support; catch up sessions if any were missed)	Yes	
Positive personal qualities of therapist	One therapist was judgemental and less flexible than the others.	Therapist not feasible
Therapist skills/background	Therapists experienced in working with this population had better retention rates.	Use therapists with experience of working with challenging families

Identified from 'Barriers to, and facilitators of, parenting programmes for childhood behaviour problems: a qualitative synthesis of studies of parents' and professionals' perceptions (Koerting, et al., 2013)

9.1.7 The TwiCs approach to providing information about interventions.

Trials using the TwiCs design take a variety of approaches to the information they provide to participants, and the extent of this disclosure about future research within the cohort varies among studies (Kim, Flory, & Relton, 2017). The majority of researchers using the TwiCs design inform would-be participants that they may be offered interventions in the future when recruiting them to the cohort, although some do not (Relton, et al., 2017).

The comparative case series of treatment by a homeopath which informed this study (Fibert, Relton, Heirs, & Bowden, 2016), told would-be participants which group they were allocated to on recruitment to the study, found that those offered treatment were more likely to join the study than those who were not. The study successfully recruited 20 participants to the intervention arm, but only 10 to the control arm (section 4.3.3). Therefore the decision was made to interpret the TwiCs design as a Dutch group using the design have done (Young-Afat, et al., 2016), by making it known to cohort recruits that they might be offered an intervention at a later date.

This was done by posting occasional articles about the interventions on the STAR Facebook page (www.facebook.com/starsheffieldADHD). Some participants mentioned that the potential opportunity to try a novel therapy influenced their decision to enrol to the cohort. However, participants recruited via flyers and ADHD support groups, who were the majority, (Figure 8) were unlikely to have seen the Facebook page when being recruited, therefore knowledge that there may be interventions did not impact recruitment significantly.

9.1.8 The validity of the trial design

This section discusses the internal, external, and ecological validity of the trial design. External validity is assessed using the PRECIS (PRagmatic, Explanatory Continuum Indicator Summary) tool (Loudon, 2015). Internal validity is assessed using the Cochrane Collaboration's tool for assessing risk of bias (Higgins, 2011). There is no tool to assess ecological validity (the extent of concordance between a trial study design and the core principles and concepts of the tested intervention).

External validity

The idea of the TwiCs design in particular, and pragmatic studies in general, is to closely mirror the experience of routine clinical practice, since the greater the similarity between patients' experiences in trials and their experiences in routine health care, then the greater the

generalisability of the trial results to patients in routine health care (Relton, O'Cathain, Nicholl, & Torgerson, 2010).

The PRECIS tool is used to assess the pragmatism of the study (http://www.precis-2.org/) by assessing domains using a Likert type scale: 1. Very explanatory 2. Rather explanatory 3. Equally pragmatic/explanatory 4. Rather pragmatic 5. Very pragmatic. It was separately scored by myself and Kirsty Loudon, who developed the PRECIS tool, and any discrepancies were resolved through discussion.

Table 36. PRECIS-2 scores assessing the external validity of the study

Domain Criteria	*Score*	*Rationale*
1 Eligibility	5	Participants with ADHD and all additional diagnoses are eligible. Only those with life-threatening illnesses or not speaking English excluded
2 Recruitment Path	4	Recruitment from domains where ADHD manifests: schools, particularly special schools, support groups, local events, looked after children, ADHD family workers, ADHD support groups. Recruitment not through the NHS
3 Setting	5	Interventions occurred in the same settings as those used by therapists in clinical practice: complementary health care settings, participant's homes, or on-line.
4 Organisation intervention	3	Some extra training provided in: CEASE methodology, NSPCC child protection, and ADHD management.
5 Flex of experimental intervention – Delivery	4	Intervention tailor made to needs of those with ADHD – no specific protocol for interventions that had to be adhered to. No specific instructions regarding co-interventions that are not allowed to be taken during treatment.
6 Flex of experimental intervention – Adherence	5	Some measures to improve adherence were used: participants were reminded about their appointments and missed appointments were re-booked. However, no action taken if appointments were missed. Non-compliers still included. Medication provided for free which is not available on the NHS.
7 Follow up	3	The interventions offered *more* opportunity for follow up than is usual in private care where clients choose how often they return. Questionnaires were completed independent of treatment by those accessing treatment and TAU participants. £10 voucher incentive to complete questionnaires.
8 Outcome	5	ADHD questionnaires are used in diagnosis and assessment of ADHD. Other outcomes were selected for their objective, evidence based relevance to ADHD.
9 Analysis	5	ITT with all available data

The two assessors concurred that the STAR pilot trial was highly pragmatic in terms of analysis and selection of outcomes, setting, and eligibility (broad inclusion criteria). Delivery was

also considered pragmatic. It was less pragmatic in terms of organisation of the intervention, since therapists had received some extra training in understanding of ADHD, and homeopaths some extra training in specific homeopathic methodologies. Return of questionnaires was considered less pragmatic since incentives and several reminders were used. Recruitment was considered less pragmatic since those seeking help generally go through their GP or the NHS, whilst only a minority search out complementary therapies.

Internal validity

The study's internal validity was considered according to Cochrane collaboration criteria (Higgins, 2011) in Table 37. Judgement was made as to whether risk of bias was high, low or unclear. It was separately rated by myself and Petter Viksveen, a colleague who has used the TwiCs trial design (Viksveen, 2017). Any discrepancies were resolved through discussion.

Table 37. Assessment of the internal validity of the study

Domain	*Risk of bias*	*Rationale*
Domain I: selection bias, random sequence generation.	low	Computer generated random sequence generated by independent researcher
Domain II: selection bias, concealment of allocation sequence	low	PI emailed age, CGI T score and medication status of participants to a second independent researcher, who allocated treatment status and an identifier according to randomised, stratified list kept in a locked drawer
Domain III: performance bias, blinding of participants and researchers	high	Neither participants or researcher were blind to allocation
Domain IV: detection bias, blinding of outcome assessment	high/low	Outcomes were collected from carers who were unblinded, and teachers who were blinded.
Domain V: attrition bias, incomplete outcome data.	low	All attrition and outcome data reported
Domain VI: reporting bias, selective reporting of outcomes	low	Outcomes reported as specified in the pre-published protocol

Validity Comparison

A strength of STAR pilot trial is its high external validity, and the high ecological validity of the interventions tested, but internal validity is inevitably low in the domain of detection and blinding: of participants, researcher and carer.

This is an issue because only once internal validity is considered adequate are other domains considered (Torgerson & Torgerson, 2008). External validity is not systematically assessed for its quality in reviews, and the PRECIS tool far less integrated than the internal validity tool. There is not even a tool to assess ecological validity.

The TwiCs design may not be considered suitable by NICE. Standardised, easily blinded interventions tested using explanatory designs are rated more highly than unblinded, pragmatic studies which are considered de facto low quality (Thornton, et al., 2013). Despite guidelines stating that they assess the 'effectiveness' of interventions, guideline developers appear to be prioritising evidence of efficacy rather than effectiveness. One of the aims of this thesis was to provide useful information to stakeholders such as NICE, but it is unlikely that the TwiCs design will be acceptable to them due to their preference for blinded, placebo-controlled designs, desire to measure specific effects, and concern with therapist effects (section 9.3.2).

It is difficult to see how this paradox can be resolved. Therapist led interventions cannot be compared to placebos. Effectiveness testing is recommended for such interventions but has lower internal validity, therefore such interventions are at a disadvantage when assessed. Demonstrating efficacy with a top down approach (does it work in clinical practice, before unpacking the black box of how/why it works) is less acceptable than a bottom up, hypothesis testing, theory generated, approach. Interventions with explanatory evidence of efficacy give credibility to clinical results. This is a problem for the acceptability of results of treatment by homeopaths but less so for the acceptability of results of treatment by nutritional therapists, which builds upon considerable explanatory evidence and theoretical models for aspects of nutrition.

Homeopathy lacks an accepted explanation for its mechanism, so evidence generated stands on shaky foundations. Clinical trials to date have attempted to address this issue by testing the efficacy of the homeopathic remedy using designs which mostly compare homeopathic remedies with placebos. However, despite the percentages of positive, negative and inconclusive results being similar in homeopathy and conventional medicine (Figure 19), this approach has neither increased the acceptability of the intervention, nor provided useful information regarding homeopathic treatment in real-life. Meta-analyses may disagree on

the conclusions they reach, but concur that trials do not represent homeopathic treatment as experienced in clinical practice (e.g Linde, et al., 1997 & Bornhöft, et al., 2006).

Figure 19. Comparison of RCTs of homeopathy and conventional medicine

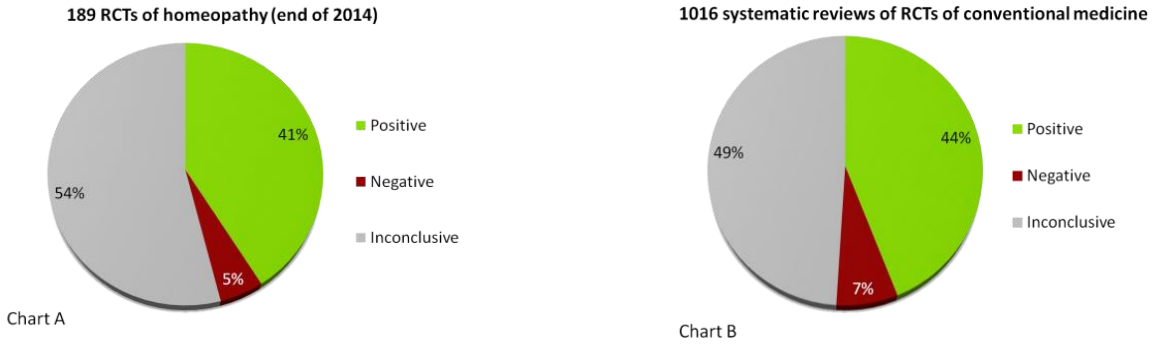


Chart A information extracted from https://facultyofhomeopathy.org/research. Chart B extracted from El Dib, Atallah, & Andriolo, 2007)

The premise of pragmatic trials is that if interventions are safe, effective, cost effective and helpful to patients, implausibility is secondary to its therapeutic benefit. There is a trade-off between the testing of specific effects, and the generalisability of results. The TwiCs trial design may not have sufficient internal validity for some assessors, nevertheless it has important contributions to make to the research canon in terms of data about recruitment, acceptability, feasibility, and the effectiveness of treatments in real-life, with the much needed emphasis on improving outcomes.

9.1.9 The feasibility of the TwiCs design to contribute to research priorities

Problems have been identified regarding the paucity of research into interventions to improve long-term negative outcomes in ADHD specifically, and child and adolescent mental health in general. The TwiCs trial design can usefully contribute to the research landscape since it can test multiple (potentially multi-component) interventions comparatively and cheaply, in at-risk, representative populations, to see whether their outcomes are improved over the long-term.

It has been identified that the evidence base for child and adolescent mental health interventions is minimal (Kennedy, 2015), particularly for the long-term effects of treatments (Fonagy, et al., 2015) (section 2.3). The majority of research funding in mental health is directed towards understanding biological, psychological and socioeconomic processes, risks and causes with "considerably less funding going directly towards the development of treatments and therapeutic interventions research" (MQ, 2015).

Interventions for child mental health are "generally complex and multi-dimensional"(Kennedy, 2009). The MRC review of Mental Health Research (Medical

Research Council, 2010) highlighted co-morbidity as an obstacle to progress in mental health research. They found that trials testing interventions in populations with mental disorders (5% according to the Cochrane database) were typically underpowered, the research was expensive, labour intensive and required specially trained staff.

The TwiCs design is particularly well placed to assess these identified research issues. Indeed it is being successfully implemented in five cohorts similar to STAR in that they have identified populations at risk of negative outcomes in areas where there is little evidence regarding the effectiveness of interventions to improve outcomes in the longer-term. They are taking innovative pre-emptive approaches to testing multiple interventions to try and improve these outcomes (studies were described in section 3.2.2).

For example, the BIBBS (Born in Bradford Better Start) cohort are considered at risk of adverse health and social outcomes which are well described. But whilst the early years have been identified as having a lifelong effect on health and well-being, there is a paucity of high quality research into the effectiveness of interventions implemented in the early years to improve later outcomes. Researchers aim to implement 22 interventions in children aged 0–3 in the areas of social and emotional development; communication and language development; and nutrition and obesity, to see whether long-term outcomes are improved.

In Canada, FORBOW (Families Overcoming Risks and Building Opportunities) recruits a cohort of offspring of parents with severe mental illness. Such offspring are well documented as being at risk of severe mental illness themselves. Currently interventions are implemented at the prodromal stage, where they are found to ameliorate but not prevent the development of severe mental illnesses. FORBOW takes an innovative approach by implementing interventions at an earlier stage, with the idea that developmental trajectories may be influenced with smaller investment and to greater effect.

FORBOW's first pre-emptive early intervention RCT is currently underway testing Skills for Wellness (SWELL), providing skill training to parents of younger children. By 2016 the cohort had recruited 306 youth, of whom 38 were eligible for the first RCT. The FORBOW research team also plan to trial courses in emotional well-being skills based on cognitive behavioural therapy for older children and youth. They selected the TwiCs design since it "saves the participants from the unnatural and possibly harmful effect of being allocated to a control group after hearing about the details of a potentially beneficial intervention" and "mirrors the practice of offering a preventive intervention to non-treatment seeking participants" (Uher, et al., 2014)

The CEDAR Project has identified an at-risk cohort of young indigenous people using drugs in Canada, and is testing an intervention to see if it reduces HIV. Another Canadian cohort of youth presenting with violence related injuries at a Canadian hospital has been created.

They are trialling an intervention (wraparound care) to see if it reduces repeat admissions. TARGet Kids! (The Applied Research Group for Kids) recruits children aged 0-5 years who present at SickKids Hospital in Toronto. It aims to conduct preventative research in the areas of obesity, micronutrient deficiencies, and developmental problems (http://www.targetkids.ca/our-research).

These studies using the TwiCs design in cohorts of children are all testing preventative interventions in at-risk populations, and this appears to be an emerging strength and potential of the design. They also have in common that the interventions they are testing tend to be complex, implemented by practitioners trying to change negative behaviours and outcomes. The utility of the design in the studies described above highlights the potential utility of the STAR cohort of children with ADHD, who are similarly at risk of negative outcomes and in need of pre-emptive strategies implemented as early as possible.

9.1.10 Cost-efficiency of the TwiCs design

This study has pilot tested two novel interventions relatively cheaply. By developing an observational cohort, and providing a research platform for multiple trials, the TwiCs design provides a cheap, cost effective way to test interventions.

The cost of running the STAR pilot trial, excluding an investigator's salary, was less than £50,000. Now that the cohort has been established, the cost of testing further interventions should be less than this sum, and certainly less than testing using a standard RCT, and having to start from scratch. Trials are expensive to conduct, and funding applications highly competitive. Because trials using TwiCs methodology are relatively cheap to conduct, interventions can be trialled which may be in the public interest but struggle to attract industrial funding.

Funding for research is highly competitive, and depends either on financial patronage of companies looking to develop products, charities, or national bodies. Currently the majority of funding is directed towards the testing of pharmaceutical medications, whilst just 0.0085% allocated to CAM interventions in the UK (Lewith, 2007). Evidence for non-mainstream interventions is less likely to be conducted due to lack of industrial funding and failure to attract national funding.

9.2 The feasibility of outcome measurement

This section discusses the thesis objective to assess the suitability, acceptability, and deliverability of the outcome measures. It discusses the means of collecting outcomes, the suitability of the measures and the statistical tests used.

9.2.1 Collection of outcomes

Collection of carer outcomes

On-line collection of outcomes by carers was feasible, and only a few participants without computers requested paper versions. Completion of on-line forms enabled on-line availability of data, which saved time and was more efficient. Missing data was reduced since participants could not continue to the next page until all items were completed. In comparison, teacher outcomes were mostly completed on paper, and had more missing items (section 7.4).

Some small adjustments are needed to the on-line website and questionnaires. Some participants completed the wrong option on-line regarding baseline, 6-month and 12-month outcome measures. This required transferral of the data by the PI. Clearer signposting is needed. Participants were only asked for the child's school information in the baseline questionnaire. This was problematic because children changed schools and teachers, so questionnaire requests were sometimes out of date, compounding the TQ return problem. School information needs to be requested each time a questionnaire is completed so school details are current.

Collection of teacher outcomes

Several problems with the collection of teacher outcomes reduce their reliability: poor return, missing items from paper questionnaires, completion of questionnaires by different teachers, and lack of completion during school holidays.

55% of teacher outcomes were returned at baseline and just 27% at 6 months. Outcomes were only requested once, by post, via headteachers, which was not sufficient. Of the 31 paired outcomes returned, 11 were completed by different teachers. Outcomes could not be completed during the summer holidays, when several children moved school and their outcomes were lost.

The poor return of teacher outcomes, which were blinded, is problematic, since blinded results increase internal validity, and some researchers only consider blinded results valid. The concern regarding unblinded results is that carers may have been invested in treatment success, (section 3.1.8) (Sonuga-Barke, et al., 2013). However, collection of teacher-rated outcomes is also associated with problems (section 3.1.8), and the difficulties identified by other researchers around procurement, multiple teachers and school holidays (Biederman, Faraone, Monuteaux, & Grossbard, 2004) were borne out in this study.

An informal summary of parent and (blinded) teacher results (Table 38) across a variety of interventions, shows that teachers, whether blinded or unblinded, tend to report higher effects of pharmaceutical medication than carers, and that carers report higher effects for non-medication interventions than teachers. There are several possible explanations for this. Some effects may be more easily identified in 1: 1 environments by those most proximal to the child, and others in group settings: for example busy teachers in large classrooms may not observe subtle changes. Children may suppress usual behaviour in some settings, for example classrooms. Carers and teachers may value different aspects and therefore rate them differently: for example teachers might value sitting still and not calling out more than carers. Carers and teachers may have differing value judgements regarding treatments. And most non-medicine interventions are implemented by carers who may be invested in treatment outcome.

Despite difficulties in collection, and possible differences in perspective, the full trial should continue to measure teacher outcomes: to provide an additional perspective; because the majority of the costs of ADHD are in education (section 2.2.6); to increase internal validity since these outcomes are blinded; and to address demand characteristics, whilst acknowledging limitations. Better collection methods must be used to increase response rates, by making several requests using various media, as was done to collect carer outcomes, and by developing relationships with schools.

9.2.2 The primary outcome

Intention-to-treat analysis assessed the effectiveness of the offer of treatment on ADHD global symptoms (CGI). That is, participants remained in the group they were randomly selected to irrespective of whether they received a treatment. The data were analysed using linear regression assessing statistical impact and standard mean difference assessing clinical impact.

Regression analysis

Covariates age, gender and ADHD severity were included in the model due to their considered influence (Conners, 2009). For example, younger children find it more difficult to stay seated in the classroom than teenagers, and differences between males and females are found for many items in statistical analyses of the Conner's data. The most accurate way to assess whether a child is typical for his/her chronological age and gender, is to control for these differences. However, only ADHD severity significantly influenced the model (Table 39), with the significance of the regression analysis driven by this. Since all groups improved, this suggests regression to the mean (section 7.5.1).

The study was not sufficiently powered to detect statistically significant differences between usual care and treatments, and total scores did not tend to find any. Mean improvements were greater in treatment groups according to carers, but with wide confidence intervals in all groups (Table 24). The un-feasible homeopath influenced the wide confidence intervals in the homeopathy arm.

Significant effects were observed in carer-rated sub-scores: the effect of treatment by homeopaths on emotional lability, and the effect of treatment by nutritional therapists on restlessness/impulsivity. Whilst these underpowered results are not robust, they are of interest, since results support therapist's opinions about the aspects their therapies are considered to address: homeopaths consider and treat emotional symptoms (section 6.5.1), whilst nutrition is considered to effect neuro-developmental pathways (section 5.2.2).

Emotional lability was measured using 3 items: temper, mood change and crying. Given the importance of this aspect, a tool measuring other facets of emotional lability would be more robust, however, there is not yet a universally accepted measure (van Stralen, 2016). The role of emotional problems is less researched and established (Mordre, Groholt, Kjelsberg, Sandstad, & Myhre, 2011), despite being a better indicator of impairments in daily living, problems in adulthood and criminality than ADHD symptoms per se. (section 2.1.1). Clinical trials may focus on measuring ADHD symptoms rather than emotional dysregulation because there is little evidence suggesting mainstream interventions improve it (Shaw, Stringaris, Nigg, & Leibenluft, 2014).

The Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004), was suggested as a commonly used tool by an expert in the field (personal communication with Professor David Coghill). It assesses the impact of six dimensions of emotion regulation: lack of awareness; lack of clarity; nonacceptance; limited access to emotion regulation strategies; difficulties controlling impulses; and difficulties engaging in goal-directed behaviours when experiencing negative emotions. However, the measure is long (40 items), and is not specific to ADHD, or to children.

The Strengths and Difficulties Questionnaire (SDQ) is designed to gather information on emotional and behavioural difficulties, (and daily functioning) but is not specifically designed for ADHD populations (www.sdqinfo.com; Goodman, 2001). It may be worth considering for future research, and is widely used in the UK. It categorises strengths and difficulties into five scales, of five items each, of which emotional problems are: unhappy, fears, clingy, somatic and worries.

The Child Mania Rating Scale, Parent Version (CMRSP) has also been used to measure emotional lability (Rucklidge, 2017). It is a 21-item rating scale based on DSM-IV criteria for mania (Pavuluri, Henry, Devineni, Carbray, & Birmaher, 2006). Items cover symptoms such as

feeling irritable, racing thoughts, rage attacks and rapid mood swings. (West, Celio, Henry, & Pavuluri, 2011).Emotional lability is an important outcome that should continue to be measured, and the search for optimum means to do so should continue.

Standard Mean Differences (SMDs)

Carer-rated SMDs were above protocol specified threshold of .3, and close to the NICE and European guideline development group's SMD of .4, considered to constitute a clinically meaningful change (personal communication with Professor David Daley & NICE, 2008). In this small pilot study, unblinded carer-rated results for both interventions appear comparable to some mainstream and non-mainstream interventions (see Table 38).

The small number of paired blinded teacher-rated outcomes available suggest that the blinded teachers observed effects of the offer of treatment by nutritional therapists which were similar to those observed by the unblinded carers. However, the teacher-rated results found for those *offered* treatment by a nutritional therapist (SMD = .39) were then reversed in those who *accessed* treatment (SMD = -.504), suggesting the results are un-trustworthy (Table 26).

To compare the results of the STAR pilot trial with other ADHD trials, an informal comparison was made by extracting the SMDs from trials or meta-analyses of mainstream interventions identified earlier in this thesis, interventions like those tested, and other homeopathy trials (Table 38). The highest level and most recently published evidence was used. Information was found by searching google scholar and web of science, and by extracting data from publications already identified in this thesis.

Large SMDs were found in two trials of homeopathic remedies (Frei, (-1.67) & Oberai (-15.6) and for the pooled results of medium doses of methylphenidate (-1.69 (teacher rating) -1.34 (carer rating). Small SMDs were found for the pooled results of PUFAs (-.28), although results were moderated by type of PUFA. Minimal change was found in one study of homeopathic remedies (Jacobs (.13); or from teacher-rated PUFAs (-.07); or from psychological interventions 3-6 months on (-.05). Table 38 contains the results of both efficacy trials (of medication, homeopathic remedies and nutritional supplements) and effectiveness trials (of behavioural interventions, and the STAR pilot RCT interventions). Effectiveness trials are expected to have smaller effect sizes than efficacy trials, (section 3.3.2) because noise is greater due to non-specific factors such as natural history of the disorder, regression to the mean, co-interventions as part of routine care outside the trial, expectations, therapist effects, ITT analysis and more (Gold, et al., 2017). Comparing effect sizes of efficacy and effectiveness trials is problematic. A more equitable comparison might be to compare the real-world effectiveness of all interventions, as the TwiCs design can.

Clinically meaningful differences

One aspect of whether positive findings from trials generalise to real world settings concerns the clinical meaningfulness of results found according to the outcome measures used. However what constitutes a clinically meaningful change in ADHD symptoms is debated. The debate centres around comparisons of pharmaceutical and behaviour change trial results and clinically meaningful differences therefore need considering within the context of validity, as discussed above. Pharmaceutical medication trials find large changes in ADHD symptoms according to validated outcome measures, but discrepancies between these and real-life clinical benefits (Hazell et al. 2005). Behaviour change programmes find small changes, but arguably useful clinical benefits.

The only published minimal clinically relevant difference for ADHD scales found (identified by Storebo, 2015) are: 6.6 points for the ADHD rating scale (scale ranges from 0 to 72 points) (Zhang, 2005); and 7 points for the child health quality of life questionnaire (scale ranges from 0 to 100) (Rentz, 2005). Both compared pharmaceutical medication with placebo over the short term in tightly controlled studies where effect sizes are expected to be high, so are not sufficiently relevant to this study.

NICE (2018 update) found an absence of values identified in the literature, For ADHD symptoms the committee therefore agreed that a >20% difference between groups represented a minimally important difference, based primarily on consensus. For other outcomes the GRADE default method is used with the proviso that any levels set can be amended subject to guideline committee discussion.

Conners (2008), who developed the CGI measure which was the primary outcome in this study, suggests that a change in classification indicates a clinically meaningful change. Classification changes occur if a T score shifts from anything above 70 (markedly atypical) to 66-70 (moderately atypical) or 61-65 (mildly atypical). This however means that a change of a few points (from 71 to 69) is considered clinically meaningful, whilst a change of 20 points (from 90+ to 70) is not. This stance is also controversial, nor is it recommended when evaluating experimental interventions, where statistical significance is recommended (Conners, 2008).

Table 38. Comparison of Standard Mean Differences for some ADHD interventions

Study description	Type	Sample size	Unblinded SMD ADHD symptoms (Confidence intervals)	Blinded SMD ADHD symptoms (Confidence intervals)
NICE (2009). Efficacy of methylphenidate (v placebo)	Meta-analysis (12 studies)	1582	Low dose = .40 (-.95, .15) Medium dose = -1.69 (-2.24, -1.14) High dose = -.84 (-1.06, -.62)	Low dose = .66(-.06, 1.37) Medium dose = -1.34 (-3.26, .58) High dose = -.79 (-1.14, -.45)
Storebo (2015). Efficacy of methylphenidate (v placebo)	Meta-analysis (19 trials)	1698		Teacher: 0.77 (-0.90 to -0.64) Carer: -0.53 (-0.78 to -0.27)
NICE (2009). Efficacy of atamoxetine (v placebo)	Meta-analysis (10 studies)	1850	Low dose = .33 (-.70, .04) Medium dose = .43(-.73, -.12)/- High dose = .59(-.71, -.47)	 Medium dose = .65 (-.87, -.43) High dose = -.59(-.71, -.47)
NICE (2009) Effectiveness of psychological interventions (v TAU, wait list, no Treatment)	Meta-analysis (10 studies)	549	.57 (-1.0, -.14)/ -.91 (-.1.23, .59)	-.25(56, .07)/-.05(-.44, .35)
Storebo (2011) Effectiveness of social skills training (v TAU)	Meta-analysis (6 studies)	515	0.02 (-0.19, 0.16)	
Sonuga Barke (2013) Efficacy of CBT	Meta-analysis (5 studies)	286	0.64 (0.33, 0.95)	0.24 (0.24, 0.72)
Sonuga-Barke (2013) Efficacy of Behavioural interventions	Meta-analysis (7 studies)	528	0.4 (0.2, 0.6)	0.02 (0.30, 0.34)
Sonuga -Barke (2013) Efficacy of Restricted elimination diets	Meta-analysis (6 studies)	200	1.48 (0.35, 2.61)	0.51 (0.02, 1.04)
Sonuga-Barke (2013) Efficacy of Artificial colour exclusion (v placebo)	Meta-analysis (8 studies)	320	0.32 (0.06, 0.58)	0.42 (0.13, 0.70)
Puri (2014) Efficacy of Polyunsaturated fatty acids (v placebo)	Meta-analysis (18 studies)	?	.28(-.42, -.13)/ -.07(-.2,.05)	
Sonuga Barke (2013) Efficacy of fatty			0.21 (0.35, 2.61)	0.16; 95% CI=0.01, 0.31

acids (v placebo)				
Frei (2005) Efficacy of Homeopathic remedies (v placebo)	RCT	62		-1.67 (-3.32, -.02)
Jacobs (2005) Efficacy of Homeopathic remedies (v placebo)	Pilot RCT	37		0.13 (-.47, .73)
Oberai (2013) Homeopathic remedy (v placebo)	Pilot RCT	54		-15.6 (-19.5, -11.6)
Fibert, (2016) Effectiveness of treatment by a homeopath (v similar time and attention)	Controlled case series	30	.71 (-1.47,.054)	
Fibert (2018) Effectiveness of treatment by a homeopath (v TAU)	RCT	50	.43 (-1.22, 4.29)	.07 (-1.67, 3.75)
Fibert (2018) Effectiveness of treatment by a Nutritional Therapist (v TAU)	RCT	50	.39 (-1.29, 5.08)	.39 (-1.75, 6.05)

9.2.3 Secondary outcomes

As well as ADHD symptoms, the STAR study measured the effects of treatments on health-related quality of life, sleep, ADHD in autism and resource use.

Health related quality of life

CHU 9D asks about worry, sadness, pain, tiredness, annoyance, schoolwork, sleep, daily routine and ability to join in everyday activities. At baseline, carers did not generally rate their children as being in pain, tired, worried or sad (Figures 21 & 22). These proxy observations are similar to those found by Peasgood et al. (2016) who asked the children themselves, which is interesting. In the STAR study the tool was not used as designed, since it was originally designed for self-completion rather than by proxy. It was originally developed for children aged 7-11 years, and has since been validated for adolescents (11-17 years). Proxy versions with children age 5-7 and under 5s have also been trialled.

Interventions had effects on more emotional items such as sadness, worry, and annoyance, but not on more practical items such as management of schoolwork or daily routine, sleep, or joining in. The items considered most problematic by carers at baseline were not significantly helped by the interventions.

It is suggested that carers' observations are influenced by the extent of their involvement (Sonuga-Barke et al. (2013). Certainly carers of children receiving treatment by nutritional therapists registered significant improvements in CHU 9D for their child (Table 26), and reported to their therapists that the whole family benefitted from implementation of their nutritional changes.

Future plans are to perform a cost-effectiveness analysis once the 12-month results are analysed. Indications are that both interventions may be cost-effective. This is likely down to the low cost of therapists who are un-regulated, increased use of on-line consultations requiring no venue hire, and the low number of hours therapists spend with participants. The cost effectiveness of NT varies depending on whether supplement costs are included.

Sleep

No improvement in sleep was found according to a single item in the CHU 9D which asks the level of problems the child had sleeping last night. A more sensitive measure of this important issue is needed to ask about other aspects such as difficulty getting to sleep, waking at night, waking early, or nightmares.

ADHD in ASCs

ADHD in ASCs has only been recognised since publication of DSMV in 2013, allowing co-occurring diagnosis. 37 children had additional diagnoses of autism, but few paired carer questionnaires were available (24 (n=6 hom; n=6 NT, n=12 TAU). Treatment by nutritional therapists was helpful for this very small sub group of children according to carers. There were not sufficient outcomes to measure teacher ratings (section 7.5.2). Results must be viewed with extreme caution.

Given that medication for ADHD for those with co-occurring autism may be more associated with side effects without commensurate benefits (section 2.3.1), it is important to continue to measure results in this sub-group, and to recruit sufficient numbers to enable robust comparisons.

Resource use

No impact on publicly funded resource use was found (section 7.7.1). It may be that the interventions did not impact resource use, the time span was too short to capture an effect, the number of participants was insufficient, or measures not sufficiently sensitive. The numbers involved with police services and social workers were particularly small. It has already been emphasised that greater effort is needed in future research to access those most 'at need', which would enable comparison of larger numbers to produce more robust results. Measurement over longer stretches of time may be needed to capture the effect of interventions on resource use.

9.3 The feasibility of treatment by homeopaths and nutritional therapists

This section assesses the thesis objective regarding the feasibility, acceptability, deliverability, safety, clinical and cost effectiveness of treatment by homeopaths and nutritional therapists for children with ADHD.

9.3.1 Case management

Regular supervision was provided throughout the trial. Such supervision is encouraged by both therapy's professional organisations, and is not a variation from usual practice. During supervision therapists needed support in understanding and managing the frequently chaotic, often troubled families.

Therapists with prior experience of challenging families were confident in their management of participants, and had higher take up and retention rates (section 8.8.4). More inexperienced therapists were challenged by the high levels of missed and cancelled appointments, changes of plans, lack of response to emails, texts or phone messages. One homeopath felt

herself unequal to management of these participants, where interestingly, all her participants reported negative outcomes (section 8.8.4).

Some experience with management of challenging families needs to be a pre-requisite for trial therapists. This need not reduce the level of pragmatism of the intervention, since it is likely that only experienced therapists would work with challenging families in real-life practice.

Treatment by homeopaths

Homeopaths were recruited from a complementary medicine clinic in Sheffield. Treatment was delivered as it would be in private practice: homeopathic remedies were individualised to each patient, and length and frequency of consultations was tailored to the needs of the patient. Homeopaths increasingly conduct consultations with patients on-line in routine practice, so the addition of on-line consultations was also in accordance with usual practice.

Homeopaths attended several workshops preceding participation in the trial concerning specific methodologies for treating ADHD cases (section 6.5). It is common for homeopaths to attend courses as part of their continuous practitioner development (CPD) so this was not necessarily a deviation from usual practice, although the courses were paid for as part of the research, which is. However, none of the homeopaths utilised the methodologies they were trained in during these courses, preferring to use the methods they normally used. Recruitment of future homeopaths will not offer this extra training as it was not cost effective and reduced the pragmatism of the intervention, but will try to recruit homeopaths who have already incorporated the techniques into their routine practice.

Treatment by nutritional therapists

The nutritional intervention was delivered by NTs who worked at the same complementary medicine clinic as homeopaths (www.wellforce.org) or in and around Sheffield. They did not attend any specialised nutrition for ADHD courses prior to the trial, however, during the trial consultants from Biocare came to talk to them, and provided free supplements and ongoing advice about supplements and a nutritional approach to ADHD. Like homeopaths they received regular supervision, where support in case management was required.

Although treatment was delivered as closely as possible to the way it is in private practice, it differed in two ways: completion of initial questionnaires, and provision of supplements. Initially therapists sent questionnaires to be completed by participants prior to their first consultation, as occurs in private practice. However, few had completed them when they attended their first consultation, and one participant dropped out post-acceptance citing the stress of having to do so. Therefore therapists completed questionnaires with partici-

pants at the first consultation, and then arranged a second consultation soon afterwards. In private practice, supplements are purchased separately by clients. For this trial they were provided free by supplement companies. ADHD families would be unlikely to purchase them.

Nutritional therapists felt trial participant's attitudes differed from those of their private clients, who, having sought them out and paid for a consultation, would follow advice, buy recommended supplements and make recommended dietary changes. Unlike their private clients, trial participants had not sought out treatment, and did not have the same level of motivation to follow advice, so when participants did not implement dietary advice, therapists relied on provision of supplements.

Nutritional therapists felt that they first needed to listen and develop rapport with carers before they could focus on nutrition, and that this was vital to retaining participation. They felt that nutrition was just one element and often secondary to other life events, which sometimes confounded any nutritional changes.

Nutritional therapists reported difficulties in treating participants with co-occurring autism (section 8.8.3) due to their particularly severe food sensitivities. However, the small number of participants with autism who received nutritional therapy reported that a dietary intervention was particularly helpful to them.

9.3.2 Consultations

Homeopathy

Trial homeopaths felt it was important to include the child in each consultation, despite my advice to the contrary which ran counter to my personal experience as a homeopath, and led to the drop out of at least one participant. Attendance of the child at every consultation can be stressful: they may hear negative things about themselves when their carer recounts their history to the therapist; carers may find it logistically difficult to bring children to all consults; it may be difficult to find care for other children in the family; children may not want to talk about their feelings, especially teenagers, and not in front of their carers; and children may not be able to sit still for the whole consultation.

On the other hand, presence of the child validates their central importance in the therapeutic process, can be valued by children, and can provide vital information to enable a suitable homeopathic prescription. Homeopaths felt that meeting with the child was important to assess changes by asking children directly and observing them, and were unconfident about relying on carer observations. But meeting carers alone provided the opportunity to get important historical information which carers may be reluctant to raise in front of the child.

On-line consultations introduced after six months, worked well for the 3/5 homeopaths who used them, and for carers. It meant homeopaths could obtain information from carer and child separately with carers relating any negative behaviour without it being heard by their child. Less commitment was required from carers compared with having to travel to attend a consultation with their child, which helped sustain participation. It allowed recruitment of families beyond Sheffield, and was cheaper, since room hire was not required. However, management of the technology was an issue for a few, and led to the drop-out of at least one participant.

Nutritional Therapy

Nutritional therapists were more flexible regarding consultation mode than homeopaths, and often conducted follow ups by telephone or on-line, without children. This was not seen as a problem for carers with younger children, since much of the consultation is between carer and therapist, and children's diets controlled by carers. However, teenagers manage their own diets, and therapists felt that only when the teenagers were engaged with the intervention did dietary changes have a chance of being implemented.

NTs reported that the opportunity to talk was sometimes the most valuable role they provided, in the absence of carer's ability to implement dietary changes.

9.3.3 Therapist effects

Both interventions were delivered by therapists, and there is potential for the treatment effect to be mediated by therapist effects. Indeed the negative effects of one therapist had a significant impact (section 8.8.1).

NICE are concerned about the generalisability of therapist delivered interventions. The director of NICE guidelines considers therapist effects to constitute 1/3 of effects seen, the other 2/3 being attributable to setting and therapy (meeting with Prof Mark Baker on 30/6/17). An example of his concern is borne out in two trials of the New Forest Parenting Programme (NFPP), which was effective when well-trained providers in an ideal setting were used, but not when tested in a more standard community setting with less highly trained practitioners (section 2.3.2). Concern regarding therapist effects influences NICE recommendations regarding interventions delivered by therapists compared to pharmaceutical medications.

The TwiCs design may provide some solutions to the vexed question of therapist effects, since testing the effectiveness of interventions provided by several standard practitioners in routine clinical practice provides more generalisable results than using well trained providers in ideal settings. Conducting sub-group analysis comparing mean outcome per therapist

would provide useful information regarding the influence of therapists on the interventions, however this will entail far larger sample sizes and increased costs beyond the budget and scope of this study.

9.3.4 Comparison of interventions

Nutritional therapy and homeopathic treatment were similar in terms of the length and number of appointments provided (section 8.8.3); in having something to ingest (a homeopathic remedy or a nutritional supplement) between consultations; and being delivered by empathic practitioners. However, they differed regarding the amount of effort required to implement the interventions. The implementation of dietary changes required considerable effort by carers unlike homeopathic treatment where little effort is required beyond occasional ingestion of homeopathic remedies. Likewise, pharmaceutical drugs require minimal effort beyond ingestion, whilst behavioural interventions require concerted effort to implement taught practices.

Consultation delivery was different: during homeopathic consultations child and carer might be asked in-depth, challenging questions, about potentially sensitive subjects, in comparison nutritional therapists asked more practical questions. Who needed to attend consultations differed: homeopaths required attendance by carer and child, whilst nutritional therapists didn't need the child to be present.

The evidence base for the two interventions also differs. Nutritional therapy is backed by explanations of mechanism and a number of trials demonstrating the efficacy of individual supplements and dietary approaches, whilst an explanation for a mechanism of action eludes homeopathic remedies. Public attitudes towards the two therapies also differ. The therapeutic modality of homeopathy is largely discredited in the UK, receiving sustained attacks, and negative press (https://www.hri-research.org/resources/homeopathy-the-debate/) whilst good nutrition is increasingly acknowledged and promoted and receives frequent positive press.

During the first month of recruitment Jamie Oliver presented a TV documentary on health and nutrition, and several participants commented that this motivated them to accept the offer of nutritional therapy. Conversely during the same time the media published reports about legal action by a sceptic group to the Liverpool Clinical Commissioning Group over its funding of referrals to the Liverpool Medical Homeopathy Service (https://goodthinkingsociety.org/projects/nhs-homeopathy-legal-challenge/). Such positions may have influenced take up of the offer of treatment in this trial since three participants refused the offer due to their doctor's disapproval during this time.

9.3.5 The acceptability of interventions to stakeholders

Nutritional interventions are already considered by NICE (NICE, 2008), and the results of this trial can contribute to the evidence base for nutritional recommendations for ADHD, which are currently mostly negative (section 5.7). However, there may be problems with NICE considering the effectiveness of a total nutritional intervention when they prioritise the measurement of specific effects, have concern regarding therapist effects, and concern regarding unregulated therapists.

It is unlikely that NICE will consider homeopathy as a therapy for ADHD in the near future. Although there are several trials demonstrating that homeopathic remedies are effective compared to placebos for ADHD, studies are small and underpowered, and an acceptable explanation of their mechanism of action according to current scientific thinking is yet to emerge. The NICE Director of Guidelines, Professor Mark Baker (personal communication) indicated that exceptional standards would be required to consider any additional treatments for ADHD since answering each question costs £30,000. He added that NICE would be extremely unlikely to consider a CAM treatment such as homeopathy due to the implausibility of its mechanism of action, and the fact that homeopathy trials are unlikely to have positive GRADE assessments.

9.3.6 Adverse events

Overall supplements were well tolerated, but three minor adverse events were probably linked to reactions to supplements: itchy skin with a magnesium spray; increased aggression with ingestion of a fish oil; and increased aggression with a multi-nutrient.

One adverse event, a skin rash, was considered to be attributable to homeopathic treatment. Those who believe homeopathy is implausible would disagree with this attribution. Homeopaths describe this as a homeopathic aggravation, (a mild, transient increase in symptoms generally associated with improvements in wellbeing) and can be a feature of homeopathic treatment) (Stub, Musial, & Alræk, 2012), since appearance of the skin rash coincided with improvements in the child's ADHD (section 8.9).

1/41 (2.4%) (hom) and 3/42 (4.8%) (NT) non-serious adverse events are far fewer than the 29% calculated in the meta-analysis assessing the benefits and harms of methylphenidate (Storebo, et al., 2015). However, the trial is not adequately powered to generalise about the safety of treatments.

9.3.7 Sample size calculation

Calculation of the sample size required for the full trial of the two treatments is based on the carer-rated effect size obtained in the STAR pilot trial of .36 for homeopathic treatment and .55 for nutritional therapy. It was decided to estimate the numbers needed for a full trial by assuming an effect size of .4.The homeopathic treatment estimate was rounded up since the effect size obtained for treatment by homeopaths may be a slight underestimate due to the negative effect of the one unfeasible homeopath. Estimations of the required sample size considered different levels of power (section 7.7). For 80% power, just over 200 additional participants are required, for which sufficient funds are available. For 90% power, 555 additional participants are needed, for which considerable investment would be required.

Based on pilot study results, attrition estimates may need adjusting. However, it was identified that substantial attrition was due to therapist's contacting strategies, and effort will be made to better manage this, so attrition estimates may not need to be increased. Therefore 40% attrition is allowed for, requiring randomisation of 166 homeopathy and usual care participants (40% of 166 = 100) where an effect size of .4 is assumed; and 150 nutritional therapy participants where an effect size of .55 is assumed (40% of 150 = 90).

9.4 Summary

This chapter has discussed the feasibility of the trial design and interventions and made suggestions for improvement in delivery. Most feasibility criteria parameters were met. The small-scale test of the design and procedures suggests that the design is feasible with minor adjustments, and that it can be implemented relatively cheaply. The primary outcome is sufficiently sensitive and measures outcomes of importance to those with ADHD. Recruitment procedures were satisfactory. Outcome collection from carers worked well after the addition of an incentive, although could still be further improved.

In comparison to effectiveness trials of other interventions, the interventions trialled in the STAR pilot trial were relatively acceptable and showed indications of effectiveness in areas of need such as emotional dysregulation (hom), restlessness/impulsivity (NT), and health related quality of life (NT). Sufficient participants were recruited to the cohort efficiently. Sufficient therapists were recruited to the trial and most were broadly competent, although they had to learn about case management of this particular patient group, at which some were better than others. Flexibility and a compassionate approach appears to have been key to retention in both therapies.

Poor return of teacher outcomes, resulting in insufficient numbers and instability of those outcomes collected was a significant flaw in the assessment of results, and is of concern

since they provide a perspective considered important by significant stakeholders. In retrospect, considerably more time should have been invested and different approaches used, to collect teacher outcomes. This is one of the main recommendations for procedure to a full trial (recommendations are described in full in the following chapter).

A feature of the trial design is that it tests the effect of the offer of treatment, as opposed to the actual effectiveness of that treatment. Results are further diluted due to attrition, non-return of outcomes and crossover from treatment to usual care. However, in ADHD particularly, where mainstream treatments offered are not particularly acceptable, and attrition and non-take up are a feature, measuring acceptability is important and provides important additional information to stakeholders.

Therapists contacting strategies contributed to non-take up. These can be improved according to the results of the pilot feasibility trial and successful contacting strategies implemented. The greater uptake of homeopathic treatment by those not on pharmaceutical medication suggests that those participants may have been looking for an alternative.

The two interventions tested may contribute information regarding effective treatments for ADHD. Prioritisation of internal validity compared to external and ecological validity by NICE may mean that the design will not be considered useful by them. However, other stakeholders such as families wanting to decide what treatments to try, and local health authorities who prioritise reducing costs and affecting long-term negative outcomes, may be more interested in this method of testing potential treatments for ADHD.

The two tested interventions now require adequately powered testing. The sample size calculation based on pilot trial data, estimates that approximately 400 more participants need to be recruited to the STAR cohort to enable an adequately powered trial of the two interventions.

There are interesting comparisons to be made between nutritional therapy and homeopathic treatment. Both are complex, one has a more established evidence base for the mechanism and aspects of its approach than the other. Both implement individually tailored advice/therapy, via therapists. The effects of treatment by nutritional therapists, where improvements according to ITT analysis by both teachers and carers was seen, may be considered the logical next step in the development of the evidence base for a nutritional approach, with therapists considered useful to provide optimum management of the intervention. The effects of treatment by a homeopath may parsimoniously be attributed to time, attention and therapist effects, particularly since no improvement in teacher outcomes was seen. However, the paucity and instability of the teacher outcomes means that no conclusions can be drawn for teacher's observations of the effects of either treatment.

It is to be hoped that implementation of the totality of a nutritional approach can be tested in a full trial, and provide useful information to NICE, who currently conclude there is insufficient information to advise on a nutritional approach. It is unlikely that homeopathic treatment will be considered by publicly funded stakeholders in the UK without much more robust evidence. However, should the effects of homeopathic treatment on emotional lability prove robust, this may provide useful information to families about an intervention to help their children's emotional dysregulation, which is often the most troubling aspect of ADHD.

Chapter 10 Conclusions, recommendations and future directions

This thesis addressed the research question: Is the TwiCs design suitable to assess the effectiveness of interventions to improve outcomes for ADHD? A small-scale test of the design and measures was conducted to answer the question, and the results suggest that the TwiCs approach to pragmatic trial design, with some modifications to its implementation, is feasible and appropriate for trials testing interventions for children with ADHD.

Recruitment to the STAR cohort was successfully accomplished ahead of time. Results from the pilot RCT give preliminary indications that the two novel interventions tested may be helpful to improve important aspects of ADHD. However, further research with larger numbers, better collection of blinded teacher outcomes, and continued collection of outcomes over the long-term is required to confirm this.

10.1 Contributions to research priorities

10.1.1 Timeliness of the research

This PhD was conducted at a time when research is questioning the hegemony of methylphenidate as a treatment option, suggesting that the benefits may not outweigh the harms, that long-term outcomes are not improved, and are associated with adverse effects (Storebo, et al., 2015; Swanson, et al., 2017). Effectiveness trials deployed in routine circumstances can aid policy evaluation and health care decisions of both providers and patients regarding pharmaceutical medication and other treatments. Such trials are being increasingly called for, particularly to assess interventions for mental health and psychological conditions (Holmes, et al., 2018; Kennedy, 2015).

The TwiCs design is well placed to address some important questions in ADHD research concerning the impact of current mainstream interventions over the long-term. Also, to test other interventions, with the purpose of improving long-term outcomes. Studies with similar aims, in different populations, have already recognised the potential of TwiCs methodology. Of particular interest are studies recruiting cohorts of at-risk children to see whether a variety of interventions may influence their potential negative trajectory. I have argued in this thesis for the same approach to be used in ADHD research, where children are similarly at risk, where the majority of research is focussed on short-term symptom relief, and where there is an unmet need for interventions to improve long-term outcomes.

With the re-publication of the seminal Schwartz and Lellouch article (1967 & 2009) identifying the differences between pragmatic and explanatory designs, health care assessors are calling for more pragmatic designs as being better suited than explanatory trials to inform

clinical practice and health policy decisions (Patsopoulos, 2011; Thorpe, et al., 2009; Conway & Clancy, 2009), whilst explanatory trials are more relevant for regulatory drug approval. However discussions with NICE directors, attendance at NICE workshops and exploration of the literature have revealed a concerning anomaly. NICE originally appraised drugs before its remit was expanded to include public health and clinical guidelines. It does not appear to have conceptually adapted its approach to accommodate these new roles assessing all types of intervention (section 9.3.5). Despite its stated objective to focus on effectiveness, it continues to prioritise efficacy research methods. For the benefits of effectiveness trials to be understood, a shift in priorities by assessors such as NICE will be required.

10.1.2 Innovativeness of the research

There are considerable pressures on our public health system, and more need than ever for effective, safe interventions and efficient, cheap research methods to help assess their clinical and cost effectiveness. This research has demonstrated that the TwiCs design provides a viable approach, and that trials can be run relatively cheaply and answer relevant research questions. It is the first time that TwiCs methodology has been used in ADHD research, and it can provide important contributions.

To my knowledge, this is also the first time that an RCT has been conducted which tests the real-life effectiveness of either treatment by a homeopath or treatment by a nutritional therapist for ADHD. The question of a homeopathic or nutritional approach as experienced in clinical practice had remained unanswered until now because trials to date measured aspects of them rather than the whole process of treatment. This doctoral work therefore contributes to the evidence base of both interventions. There are preliminary indications that both interventions may have a role to play in the improvement in long-term outcomes of those with ADHD. The research provided preliminary insights into their acceptability, safety and effectiveness adjunctive to usual care.

The STAR project furthermore demonstrated that the TwiCs design is an appropriate research design to capture the effects of CAM therapies. This can resolve the discrepancy between what clinicians and patients report anecdotally, and traditional placebo-controlled RCT design results. The design has now been used to test the effectiveness of treatment by a homeopath for menopausal hot flushes (Relton, O'Cathain, & Nicholl, 2012), irritable bowel syndrome (Peckham, et al., 2014), and depression (Viksveen, Relton, & Nicholl, 2017), and it has been used to test the effectiveness of acupuncture for lower back pain (Dascanio, Birks, & Torgerson, 2011). This is the first time it has been used to test the effectiveness of nutritional therapy.

This study contributes to the development of the TwiCs approach, which is gaining credibility in other domains and becoming established in the research landscape as a pragmatic trial

design suitable to answer real-life questions of interest to stakeholders in a wide variety of fields, across a wide age range, and testing a wide variety of interventions to improve long-term negative outcomes. Cohorts of the elderly have been created and interventions implemented to prevent or aid their recovery from hip fractures and falls. Cohorts of those suffering from particular illnesses have been created and interventions such as exercise and novel surgical procedures implemented. Cohorts of children at risk of negative long-term outcomes have been created, and interventions implemented such as CBT, wraparound care, provision of health care via mobile phones, and skills for wellness teaching (https://www.TwiCs.global/use-of-the-design).

10.1.3 Learning from the research endeavour

This thesis was motivated by the desire to conduct appropriate academic research according to approved methods into an intervention I have perceived that patients find helpful. Through doing this research I have understood and learned a great deal about research processes and health care decision making.

I have gradually assimilated and exemplified an understanding of pyramid of evidence creation as my research has progressed. Initially I thought collecting the outcomes of patients receiving homeopathic treatment sufficient to demonstrate the effectiveness of treatment. Then I understood that these patient outcomes needed a comparator, and baseline was not enough. Having provided a comparator I then realised that this was not sufficient, and that participants needed to be randomly assigned. So for this PhD I conducted research in randomised participants. This has led to the discovery that randomised outcomes may need to be blinded for results to be taken seriously by most ADHD researchers and assessors. I predict that future research with blinded outcomes will not be sufficient either, and these results will then need to be replicated, and in larger numbers. I have understood that research is a process with no finite conclusion.

I have also understood the difficulties inherent in capturing the non-specific effects of non-specific treatments. I have developed an understanding of the rationale for, and methods to reduce bias and subjectivity in research, but have observed that these methods are sometimes unequally applied. I have also observed the influence of market forces on opinion. Although the trial design and interventions attract interest in some venues, such as recently at an international ADHD conference largely attended by clinicians (http://adhdcongress.co.il/), it has been frustrating to understand the higher hill which non-pharmaceutical interventions have to climb to be recommended by NICE, our national health care regulator.

10.1.4 My contribution to the research endeavour

At the beginning of this doctoral research I explored appropriate research designs to test the effectiveness of homeopathic treatment. The majority of published research into the effect of 'homeopathy' compares homeopathic remedies with placebo remedies. I realised that such tests were not appropriate to answer the question of how effective treatment by a homeopath is to patients. Having selected a TwiCs approach, and understood its strength as a platform for research evaluating multiple interventions, I searched for another promising intervention to demonstrate this aspect of the design. I selected treatment by a nutritional therapist, where again, the effectiveness of a nutritional approach for patients had not been tested in trials to date. The intervention also provided similar time and attention to that provided by homeopaths.

Having selected the interventions, I then needed to identify key stakeholders involved in the care of those with ADHD and the outcomes of importance to them, decide how to best measure those outcomes, and create a simple questionnaire to do so. Having done this, written and published the study protocol, acquired the necessary permissions, and subjected the proposal to external scientific review, the majority of my time and energy was spent recruiting participants to, and managing the administration of, the STAR cohort and the first pilot trial. I visited schools, networked with ADHD stakeholders, attended conferences and embraced all recruitment opportunities that offered themselves.

On recruitment, I extracted the age, ADHD status and gender of participants who had completed baseline questionnaires, and sent the information regarding those who were eligible to the independent statistician for randomisation. Recruitment of participants to the trial involved posting out letters to those offered treatment and following up with telephone calls giving them the details about their therapist. I recruited local therapists, and was in regular contact with them for the duration of the trial: supervising them monthly; providing them with participant contact details; and receiving reports from them after each consultation.

Recruitment was on a rolling basis, which meant all correspondence relating to each participant at baseline, six and twelve months required individually requesting at the appropriate time. Carer requests often needed following up with multiple reminders. Once questionnaires were returned, participants needed to be sent thank-you vouchers. Sending letters and questionnaires to schools required identification of the current headteacher and correct, full address of the school. Further reminders were not sent to schools due to the administrative burden, and the assumption that teachers would efficiently return questionnaires. In retrospect this was an erroneous assumption.

Data organisation and analysis made up the last stage of the research process, and was largely conducted alone, with some help and advice from the University Maths and Statistics help (MASH) service and supervisors.

The following sections relate the results of the STAR project to the general body of knowledge on the subject and prevailing research environment and makes recommendations for future directions.

10.2 Strengths and weaknesses of the TwiCs design

10.2.1 Challenges of taking a pragmatic approach

Whilst reviewing the evidence base it became clear how difficult it is currently to compare the effectiveness of interventions to improve outcomes for ADHD. Different trial designs are used, of varying length (usually short), in varying populations, measuring various outcomes, to test different types of interventions. The clinical meaningfulness of trials (i.e. their external and ecological validity) is not systematically assessed, and the PRECIS tool assessing external validity far less used or respected than Higgins' internal validity tool. 'Quality' in publications refers only to risk of bias, so trials with good external validity are described as 'poor quality', but trials with poor external or ecological validity do not necessarily receive negative summation.

Most trials of pharmaceutical medicines compare them to placebo medicines in carefully controlled conditions. The other category of intervention offered – behavioural change programmes – are tested in clinical practice, in comparison with usual care or baseline. The two types of testing are expected to differ in their levels of internal, external and ecological validity, and their effect sizes (effectiveness trials are expected to have smaller effect sizes (section 3.3.2)). Carefully controlled conditions may maximize potential to detect an effect, but "the attempt to achieve methodological purity tends to result in clinically meaningless results" (Witt, et al., 2012).

The different designs answer different questions. However, double-blinded, placebo-controlled designs are being used comparatively to make decisions about effectiveness in clinical practice. This means that interventions which can be best tested using such designs (pharmaceutical medicines) tend to be preferenced compared to those which can't (therapist led interventions) (section 3.1.7). This appears to be paradoxical and not in the interests of improving patient outcomes, and may explain why negative outcomes for ADHD are not being affected despite numerous studies demonstrating the short-term effectiveness of pharmaceutical medications compared to placebos, and resultingly large increases in prescriptions (section 2.3.1).

The decision to employ effectiveness testing rather than efficacy placebo-controlled testing was a decision to conduct pragmatic research with practical outputs. The more used and respected double-blinded placebo-controlled RCT design was clearly unsuitable because not only does it not measure real-world effectiveness, it is unsuited to the testing of therapist led or complex interventions. However attempting to achieve full generalizability in a trial design can result in unreliable results and potential measurement of other factors, therefore achieving a creative tension between the two is crucial, and this is what the TwiCs design importantly attempts to do.

The STAR project is unusual in not testing the specific effects of therapists, supplements/dietary advice/homeopathic remedies etc. for those with ADHD. These effects are of interest to health care assessors in the UK (NICE) and those sceptical of the benefits of homeopathic remedies. They are unlikely to consider evidence about the effectiveness of the interventions tested sufficient without prior evidence of an explanatory mechanism for specific elements such as those described above, or demonstration that more parsimonious explanations are not responsible for effects observed.

Like any pragmatic trial, there is inevitable variation (noise) amongst participants since conditions are less tightly controlled. There is potential for variables outside the trial to influence outcomes and acceptance. For example, media and mainstream medical opinion may have influenced acceptance rates. Participants may have tried other interventions or changed medication dosage during the trial which may have influenced their measurement of outcomes. Outcome completion by different teachers and children changing schools may have influenced the precision of teacher outcome completion.

10.2.2 Benefits and challenges of using the TwiCs design

Benefits

The TwiCs design is suitable to test multiple interventions comparatively and provide a good balance of internal, external and ecological validity. Regarding internal validity, biases are equally distributed across groups, and the more trials conducted using this method, the more generalizable and robust the results become. For example, in tests of therapist led interventions, potential biases such as Hawthorne and practitioner effects are equally distributed across trials of such interventions. The design is appropriate to assess the comparative effectiveness of all interventions, be they complex, holistic, therapist led or pharmaceutical.

The TwiCs design enabled speedy recruitment of sufficient numbers, comparing favourably with recruitment to comparable trials (Table 34), to UK trials in general, and to the comparative case series preceding this trial (section 4.3). Full, fast and efficient recruitment is emerging as a significant benefit of the design (Viksveen, Relton, & Nicholl, 2017).

Recruitment may have been easily achieved because participants' experiences were closer to real-life practice than conventional designs. For example, because they were not initially told they may receive an intervention and then later told they wouldn't, the risk of resentful demoralization in the usual care group was reduced (Torgerson & Torgerson, 2008). Nor was any deception involved, or participants told they may receive a placebo treatment, where patients have been found to become frustrated (Dunn, et al., 2003). Trial conditions were as close as possible to what patients could expect if they consulted therapists in clinical practice, and health care assessors might expect were they to commission the treatment, and this can contribute important information to stakeholders and the ADHD research canon.

ADHD is associated with negative outcomes that assert considerable impact on society. There is a need to focus on improving those outcomes. This can be done by testing the potential of interventions in real-life populations, and measuring important objective outcomes over the long-term in a representative ADHD population. TwiCs methodology provides an innovative, robust means of assessing the usefulness of interventions over the longer-term.

Challenges

The TwiCs design is novel and unusual, and challenges conventional ways of testing interventions. Until established, some may find it unacceptable. Consort guidelines for TwiCs are in development, but until published, there are no guidelines on how to report trials conducted using the design.

The trial design measures the effect of the offer of treatment, i.e its acceptability. The effectiveness of the treatment itself is a secondary analysis. Those deciding whether to commission treatment, such as NICE, may be more interested in the potential treatment benefit to patients as opposed to its acceptability, as may those looking to promote the benefits of their therapy. However, measuring acceptability is of particular importance in the field of ADHD research (section 9.1.2).

Non-acceptance and non-compliance is a key challenge to the use of the design. Standard designs screen out potential non-compliers and non-acceptors prior to randomisation. Use of the TwiCs design runs the risk of a type II error due to lower follow up rates and crossover from treatment to usual care (Viksveen, Relton, & Nicholl, 2017). ITT analysis estimates the effect of the offer of treatment, but instrumental variables analysis is recommended as a secondary analysis. This complier average causal effect (CACE) analysis considers baseline values to assess the effectiveness of treatment received. It compares offer group participants who have received the intervention with participants not offered the intervention, but who would have received the intervention had they had been offered it (Greenland, 2000).

Collection of blinded outcomes is not an intrinsic aspect of the TwiCs design, indeed is not an aspect of pragmatic designs in general. However, without measurement of blinded outcomes, and/or prior efficacy evidence, there are those who will not consider results attributable to treatment. It is therefore questionable whether testing treatments using the pragmatic TwiCs design is appropriate without prior explanatory evidence.

10.3 Interpretation of results of the first RCT in the STAR project

In this small pilot study, carer-rated unblinded ITT results suggest both interventions may be helpful for different aspects of ADHD, and effect sizes are comparable to some other mainstream and non-mainstream interventions (Table 38). Blinded teacher results were few in number, and not robust (section 7.5.1). The paucity of teacher returns is a significant failing of this research because the inability to consider blinded teacher results reduces the internal validity of the study.

The results for both interventions are similar according to the carer-rated primary outcome (ITT analysis of CGI total score). Treatment by nutritional therapists showed a medium effect of the carer-rated primary outcome (SMD .388) and in the sub-score restlessness/impulsivity (SMD .623). The results of treatment by homeopaths also showed a medium effect size for the carer-rated primary outcome (SMD .425), and the sub-score emotional lability (SMD .793). Despite results being similar, treatment by a homeopath and treatment by a nutritional therapist are likely to be viewed differently since one intervention is more plausible than the other.

10.3.1 Treatment by a nutritional therapist

The results for nutritional therapy will hopefully to contribute to the on-going discussion by NICE regarding nutrition, particularly if an adequately powered full trial can now be conducted. The design meets NICE's stipulated objectives, which are to be a controlled RCT measuring ADHD symptoms, with a usual care comparator, and reaches the GRADE default minimally important difference of -0.5/0.5 standard deviations for several outcomes (Hopkins, 2015).

It is surprising that there has not already been a trial of a nutritional approach for ADHD, since it is the logical next step in building evidence; the question is theoretically of interest to stakeholders; and the NICE guidelines already recommend asking about nutrition and referral to a dietician where relevant, although this policy is not evidence based.

There are numerous trials prioritising understanding of mechanisms of action and the efficacy of individual elements or specific approaches, for which there is weak evidence. Such studies provide explanatory evidence and theoretical models for aspects of nutrition which

the STAR pilot trial builds upon. The STAR trial suggests a combined, total nutritional approach may have a larger, composite effect.

10.3.2 Treatment by a homeopath

Considerable opposition exists to this therapy, and much debate about the evidence base, so the results for treatment by homeopaths are unlikely to be considered by NICE. There will continue to be those who will not be persuaded of any clinical improvements until a plausible explanation for its mechanism of action is found and homeopathic remedies have irrefutably been shown to work better than placebo remedies. To date just four RCTs have been conducted testing the clinical efficacy of homeopathic remedies for ADHD, of which three found positive results (chapter 4).

Interventions with explanatory evidence for their mechanisms of action lend credibility to clinical results. So-called energy medicines such as homeopathy, who cannot explain their mechanisms of action using concepts in line with current scientific understanding, are given more parsimonious explanations for any effects found. However, it could be argued that if an intervention is safe, effective, cost effective and helpful to patients, its implausibility may be considered secondary to its therapeutic benefit.

Advocates of the scientific method may not consider any results using the TwiCs trial design sufficient to generate evidence about the effectiveness of treatment by homeopaths without prior evidence of an explanatory mechanism or demonstration that more parsimonious explanations are not responsible for effects observed. ADHD stakeholders however, may take a more pragmatic approach, and prioritise improved outcomes, safety and reduced costs over explanations.

10.3.3 Implications of the results for ADHD treatment

The two interventions tested were selected: because carers are turning to them; because there is preliminary evidence supporting them; because there is building evidence that mainstream approaches are not making a substantial difference to outcomes and therefore novel approaches require exploration; and because a holistic approach (as compared to a unitary approach), may be appropriate to improve and sustain long-term outcomes in this heterogeneous condition. The first three reasons have been discussed elsewhere in this thesis (sections 1.5.3, 4.2.8, 5.5 & 1.5.1). The fourth reason is briefly discussed here.

ADHD is characterised by heterogeneity, multi-morbidity, and the influence of diverse aetiologies. Holistic or ‘whole systems’ approaches suggest interconnectedness and non-linear outcomes (Koithan, Bell, Niemeyer, & Pincus, 2012), in contrast with a biomedical model presupposing unidimensional simple causes and individually testing single aspects. Holistic

approaches take account of all aspects of patients as individuals, assessing them on mental, emotional, physical and general levels, accommodating heterogeneity, aiming to improve overall health and stimulate self-cure.

Improving long-term outcomes may be better achieved by using a multi-modal approach. For example, focussing on improving long-term overall health as well as on symptom reduction. Indeed a multi-modal approach is recommended in the European Clinical guidelines (Taylor, 2004). The effects of mainstream treatments tend to disappear over the long-term, whilst in two small studies of homeopathic treatment improvement continued for eight years and one year respectively (von Ammon, et al., 2012 & Fibert, Relton, Heirs, & Bowden, 2016). These underpowered results need validating. With regards to nutrition, studies increasingly show that improved nutrition impacts on all aspects of health.

10.4 Recommendations for improving the STAR project

This section makes some practical recommendations for improving the delivery and performance of the STAR project (cohort and trial) emerging from the results and discussion concerning recruitment, outcomes, interventions and the trial design.

10.4.1 Recruitment to the STAR cohort

Future work should prioritise recruitment from 'hard to engage' families (predicted by low income, single carer status, education/occupation, family size, minority status, severity of child's behaviour, maternal psychopathology and maternal age (Doherty, Stott, & Kinder, 2004). Collection of data regarding these predictors can measure the extent to which this occurs. Not only are such families most in need of effective help, but given that recruitment to the STAR cohort was satisfactorily achieved, and recruitment to trials is considered relatively problematic, this can explore whether recruitment is a factor of recruiting easier families, or whether it continues to be successful with more 'difficult to engage' families.

For similar reasons, effort should be made to recruit those involved in the criminal justice system or in care. This may necessitate applying for NHS ethical approval, to allow access to 'looked after' children under the care of Sheffield city council and a large ADHD patient data base of over 2,000 registered with CAMHS, NHS Sheffield; may lead to recruitment of a more representative sample; and may improve the acceptability of the STAR project to ADHD stakeholders, many of whom work within the NHS. However, it could restrict the scope and freedom of the project by limiting recruitment to NHS approved locations, and obtaining NHS ethical approval can be time consuming, so the benefits and disadvantages of such a decision would need to be weighed carefully.

Recruiting larger numbers of those with co-occurring autism and ADHD is also required to see if interventions may be helpful in this 'at need population'. Recruitment strategies should continue developing ways of improving understanding of those with ADHD, not only because this has been identified during the STAR project as a need, but also to contribute to recruitment. Application is currently being made for funding to develop the 'Lost Voices' video and workshops and tour UK schools with them. If successful, this link with schools may have the added benefit of improving understanding of how to best obtain teacher outcomes.

10.4.2 Adherence to the STAR trial

If adherence to the trial is to be improved, it needs to improve the treatment accessing rates of those accepting but not accessing treatments. To this end, contacting strategies need improving. One suggestion is to ask all therapists to employ the successful strategies used by some other therapists, namely use of different means of contact, and at different times of day, and reminders about consultations the day before appointments. Another suggestion is for consultation dates to be arranged by the PI when participants are first telephoned to be offered a treatment rather than requiring contact by participants with an as then unknown therapist, which may be off putting. Another suggestion, funds permitting, is to employ an administrator to be the main point of contact with participants, who can offer them the treatment, get to know them, understand their preferred communication modes and times, and liaise between therapists and participants regarding consultation dates and times.

To improve the collection of carer and teacher outcomes, those who have not responded to requests to complete questionnaires could be telephoned and questionnaires completed over the telephone. Another suggestion is to improve communication with all participants, but particularly those offered treatments, regarding the importance of regular completion of the STAR questionnaire regardless of their decision regarding treatment. Participants could be made better aware of this when they recruit to the cohort. This may result in participants dropping out at this stage rather than post acceptance, which would reduce pressure on therapists, and provide explanations for drop out (un-explained when they become uncontactable). Qualitative work with participants might further enlighten this issue.

Regarding consultations, eight available sessions over one year are more than tend to be accessed by private patients, so offering less than 8 sessions would better represent real-life care and make the trial cheaper to run, since consultation cost is the main trial expense. Participants could be offered five sessions further apart after the first three appointments, instead of eight appointments at 6 weekly intervals. Future research might explore the minimum number of consultations necessary to make the intervention cost-effective.

10.4.3 Outcome collection and measurement

Means of collection

Outcomes are collected three times over the course of one year. Ideally, they would be regularly collected over the longer term. Regular, annual collection might improve seasonal variation problems, however, it would not improve the problem of completion by different teachers, since most children change classes annually.

There are problems regarding the consistency and sensitivity of observation with teacher outcomes which raise concerns about their reliability even were they able to be collected. If money was no object, independent assessment by a different blinded source, such as a clinician, might enable more sensitive blinded observations. One study using the TwiCs design in a cohort of children at risk of mental health problems, invites all participants for such an annual, day long clinician assessment (Uher, et al., 2014). However, this is impractical both financially, and geographically. Therefore it will be important to improve the return of teacher outcomes in future research, despite concerns regarding their reliability. Blinded outcomes and a teacher perspective are important, not least since this is where the majority of the cost of ADHD is incurred (section 2.2.6).

Requesting teacher outcomes just once by post was insufficient. In the future, after the initial letter has been sent, the school office should be rung to notify them of the letter, and to make initial contact. If possible, the teacher's contact details should be obtained during this phone call (email addresses and telephone numbers), so that outcomes can then be requested from the teachers themselves in a variety of ways, rather than in a letter via the head-teacher as currently occurs. Teacher contact details are not available on school websites. Teachers should also be better directed towards on-line completion, where less missing items occur. The link was provided in the letter, but not used. A direct link in an email may be better acted upon.

6 and 12-month carer questionnaires need altering so that the child's school and teacher details are requested every time (currently they are only requested at baseline) in order to have up to date information about the school, teacher and educational status of the child. The signposting for completion of baseline, 6-month, or 12-moth questionnaires on the STAR website also needs improving, since several participants completed the wrong questionnaire.

Outcome measurement

A more sensitive measure of sleep difficulty might better capture this important outcome. It might include questions about difficulty getting to sleep, waking early, waking during the

night, nightmares etc. However, care must be taken to balance the need for information with ease of completion in order not to discourage participants from completing questionnaires.

It might be worth measuring autism symptoms in those participants with co-occurring autism. It may be that their global autism symptoms as well as their ADHD may improve with treatment. Since this would not be relevant to all STAR cohort participants, participants with co-diagnoses would need to be contacted, and asked to complete an additional measure such as the Autism Treatment Evaluation Checklist (ATEC) (Magiati, Moss, Yates, Charman, & Howlin, 2011).

How to best measure emotional lability requires further thought. For this study a sub set of the CGI was used. Since it only measured three aspects, it may not capture the breadth of emotional dysregulation in ADHD. Some potential measures were discussed in section 9.2.2. There is a need for agreement regarding the definition and measurement of emotional lability since there are currently discrepancies across measures: the SDQ (Goodman, 2001) categorises temper tantrums as a behavioural problem, whereas the CGI (Conners, 2008) categorises it as an emotional one. CGI (carer) considers 3/10 items to be measures of emotional lability, but CGI (teacher) using the same scale, considers 4/10 items to be measures of emotional lability and 'demands must be met immediately' is categorised as an emotional problem.

Should emotional lability continue to be measured via the CGI, this will necessitate the continued use of the CGI outcome measure. This measure was sufficiently sensitive and appropriate to measure the effectiveness of the non-specific interventions, whilst the other measure (SNAP) trialled, may not have been, although there were too few results to be sure. Despite SNAP being cheaper, evidence favours the continued use of CGI. The fears of the steering committee chairman that CGI results may not be considered adequate to demonstrate improvements in ADHD symptoms (a further reason for the inclusion of SNAP) were unfounded. The measure was not questioned at any conferences where the protocol or results were presented.

Some outcomes, such as levels of criminality and exclusion might be more accurately measured by accessing national registers rather than asking carers or teachers. Accessing educational records can also provide an opportunity to measure whether interventions improve educational attainment.

10.4.4 The Interventions

Further work is needed to explore for which sub-groups treatments might be most effective, and for which aspects of ADHD might they be most helpful. It is self-evident that nutritional

therapy may be helpful for those children with digestive problems and less so for those without them. Homeopathic treatment may be helpful for those with accompanying emotional problems, but less so for those without them. How to identify these sub-groups needs exploring. One suggestion could be to ask specifically about gut dysbiosis and emotional lability in questionnaires. Another suggestion could be to ask all participants to complete MYMOPs (currently only treatment groups are asked during consultations), and identify those with gut dysbiosis and emotional lability via their MYMOP responses (section 10.4.3). Another suggestion to recruit those with emotional problems might be to target recruitment at those involved in criminality, where research suggests that the emotional element predicts criminality (Young, Taylor, & Gudjonsson, 2016). This would have the added benefit of specifically targeting those most at need.

The therapists

Improving therapist knowledge of ADHD may improve contacting strategies, case management, intervention acceptance, participant retention and therapist wellbeing. Continuing to provide a pre-trial ADHD workshop and NCPCC risk course for therapists is indicated. Based on therapist's experiences in the first STAR trial, the course should focus more on case management to prepare therapists.

Regular supervision is also still indicated to support therapists in managing their patients. Such supervision is often a component of working with troubled families. For example when I worked with school refusers at St George's Hospital psychiatric unit I received daily supervision. Therefore such support should not reduce the level of pragmatism provision. Ideally therapists should have experience of working with 'troubled' families, either as homeopaths or in other disciplines such as social work or education, in order to be able to communicate effectively with them, and manage the levels of disorganisation which may manifest.

It is not recommended that homeopaths gain extra training in specific homeopathic methodologies, since the methods learned were not accessed. Not only will this save money, it will make the trial more pragmatic.

Recruitment of therapists working in the NHS could explore the feasibility of treatment within the NHS. NHS doctors who are also homeopaths in Bristol (The Portland Centre for Integrative Medicine) and London (The Royal London Hospital of Integrative Medicine) are interested in participating. There may be impediments to using nutritional therapists within the NHS, where nutritional advice is mostly provided by dieticians, who would therefore need to be recruited instead of nutritional therapists. Exploration of the effectiveness and cost-effectiveness of such NHS clinicians compared with professional therapists would be of interest. Practitioner costs of those working outside the NHS are less, and such practitioners an untapped resource.

Questions about therapist effects are not answered using the TwiCs design and were of concern to the NICE director of guidelines. Testing multiple therapist led interventions as experienced in clinical practice can distribute therapist effects across those interventions. Using multiple therapists, potentially randomly selected from a general registry of therapists can also address this concern.

The consultations

Future recommendations are to keep intervention delivery pragmatic and flexible, and to continue to use multiple consultation modes, according to carer preference. As long as therapists do not compromise their ability to deliver good treatment, they should offer flexibility about who attends consultations and venue, particularly regarding attendance of the child at every consultation, which may lead to greater retention of participants. It appeared that the introduction of skype/VSee consultations made life easier for families, possibly because it required less effort to attend.

Therapists should continue to implement changes pragmatically according to the tolerance of the carers and their children. The extent to which participants are able to follow advice, particularly nutritional advice, should be monitored more systematically, since such information is of interest.

10.4.5 The trial design

The research question asked whether the TwiCs design is suitable to assess the *effectiveness* of interventions. In reality, the primary analysis using ITT is the effect of the *offer* of interventions, that is their *acceptability*, and effectiveness is a secondary outcome. Analysis if the full trial should include CACE analysis as a non-biased way of assessing the actual treatment effect (Hewitt, Torgerson, & Miles, 2006).

Factors not related to treatment acceptability, which appear to influence acceptability, need to be taken in to account, such as setting, media influence and the amount of effort required to implement interventions. A future development of the TwiCs design might compare these across studies to provide more generalised information to trialists.

Mainstream treatments for ADHD, such as pharmaceutical medication and behavioural change programmes, as well as other potential interventions should be tested using the TwiCs design so they can be compared and their real-world long-term effectiveness assessed. Considerable economies of scale can be achieved should multiple trials be conducted.

A final recommendation is to promote the benefits and approach of TwiCs methodology and draw attention to shortfalls and inequalities of currently preferred designs. This can be done by highlighting the successful use of the design in other similar cohorts, and through academic publications, presentations, and discussions with NICE.

10.5 Real-world/political context

The aim of this thesis is to test whether the TwiCs design is feasible to generate evidence to improve outcomes for ADHD. Although the design appears feasible and useful, it may encounter obstacles due to the current evidential paradigm and real-world situation. In this next section, I will describe some examples hindering both the generation and acceptance of evidence.

I took a more positivist perspective in conducting empirical research (section 1.2.4), with the understanding that Evidence Based Medicine (EBM) and the scientific method inform health care decisions. However, over the course of this PhD I have observed interpretivist influences on EBM.

10.5.1 Bias against homeopathy

Considerable resources are employed by a small group of very effective detractors in the UK to influence public, media and government opinion against homeopathy. They largely refer to two biased documents: a meta-analysis by Shang et al. (2005) which fails sensitivity analysis (Lüdtke & & Rutten, 2008); and a House of Commons technology report (House of Commons Science and Technology Committee, 2010) which is based on Shang et al, and was dismissed by the department of health in an early day motion. Nevertheless detractors have succeeded in creating an environment where debate and media coverage is one sided and limits the acceptability and publication of any positive homeopathy results generated.

For example, I co-authored a systematic review of homeopathy for depression which was initially accepted by sub-editors of a well-known journal but then rejected by the editor. He provided a negative opinion piece and a blog to justify the journal's stance that homeopathy is not an effective treatment for any health condition. In other words, only articles informing the journal's interpretive stance were acceptable. In another incident, I was interviewed on BBC Oxford describing my research, whereupon a well-known sceptic blogger complained to the BBC, who responded to his complaint by assuring him that homeopathy will never again be discussed without the prior proviso that it does not work.

10.5.2 Industry bias

The many industry funded trials testing the short-term efficacy of drugs for ADHD (Storebo, et al., 2015), and other conditions (Booth, 2010) suggests that financial gain and desire to promote products may be influencing trial design. Although the aim of health interventions should be to improve the health of the target population, other drivers are influential and important questions are not being addressed. It is argued that the evidence based 'quality mark' has been misappropriated and distorted by vested interests (Greenhalgh, Howick, & Maskrey, 2014).

It is suggested that even publicly-funded research is not being orientated in the best interests of patients or public health (Davis, 2015), with resources allocated to drug discovery and development to the neglect of other types of investigation (European Commission, 2007; Food and Drug Administration, 2004; Kanavos, et al., 2010). This means there may be poor correspondence between both public and private-sector research priorities and the concerns of patients and clinicians.

Despite numerous trials, questions still remain concerning the effectiveness of pharmaceutical products, that is, do they work in the real-world with the average patient and improve long-term outcomes? This latter question, whilst of interest to stakeholders, may not be in the interests of drug companies looking to showcase their product, best showcased using short-term, tightly controlled trials, but not longer-term trials of real-world effectiveness. Nor may it be of interest to scientists looking to further scientific knowledge. Whilst the TwiCs design provides a comparatively impartial way of testing interventions with the aim of improving outcomes for children with ADHD, it may conflict with these other drivers.

Evidence is emerging that commercial conflicts of interest suggest we cannot be confident of the results of industrially funded trials. John Ioannidis suggested that "the greater the financial interests in a given field, the less likely the research findings are to be true" (Ionnadis, 2005). Professor Gotzsche claims much of the behaviour of the pharmaceutical industry fulfils the criteria for 'organised crime' (Gotzsche, 2013). The most recent Cochrane systematic review concluded that all 185 double-blinded, placebo-controlled RCTs of methylphenidate were at high risk of vested interest (Industry) bias and selective reporting bias (Storebo, et al., 2015). The editor of the New England Journal of Medicine states that "it is no longer possible to believe much of clinical research published", giving as examples two prominent ADHD researchers, Biederman and Wilens, (both cited in this PhD) investigated for not disclosing 1.5 million dollars received from pharmaceutical companies (Angell, 2009). Angell further attests that trials are biased through use of designs chosen to yield favourable results for sponsors.

The predominance of pharmaceutical medication as the treatment option for ADHD despite NICE's recommendation that it only be used in severe cases (NICE, 2008), the lack of clear evidence that long-term outcomes are effective, and the promotion of the blinded placebo-controlled RCT trial design, suggests vested interest bias may be at play in the assessment of interventions for ADHD. The possible influence of vested interests are a further reason for using a trial design such as TwiCs to efficiently and objectively test multiple interventions. Whilst the TwiCs design has important contributions to make to the research canon, considerable work may be required to promote its benefits and draw attention to shortfalls and inequalities of currently preferred designs and vested interests.

10.6 Future directions and recommendations

The STAR project demonstrated the feasibility and utility of the TwiCs approach to pragmatic RCT design for children with ADHD. It is my aspiration to develop the STAR cohort as a facility, so it can continue to be used to rigorously evaluate a variety of main and non-mainstream interventions in a timely and efficient manner using TwiCs methodology, to clarify whether they improve both short and long-term outcomes for children with ADHD.

This will entail expanding the STAR cohort, focussing on recruitment of those most at need: teenagers, hard to reach families, those with co-occurring autism, looked after children, and those involved in criminality. Effort should also be made to recruit those with multiple co-morbidities to the cohort.

Focus should be on aspects of ADHD which presage poor outcome, such as emotional dysregulation and criminality. This can be done by exploring how to best measure changes in these aspects in future questionnaires, and prioritising the testing of interventions which may be helpful in such populations. This can contribute evidence-based information to the discussion of how best to improve outcomes for those with ADHD. Development of relationships with academics in the field through academic publications and presentations and promotion of the benefits of a TwiCs approach can further support this.

There is sufficient preliminary evidence now to justify a full trial of the two piloted interventions, with modifications based on the findings from the feasibility study. Applications have been made to a variety of sources for funding to do this, and funding received from the British Homeopathic Association to enable a full trial of treatment by homeopaths to now be conducted. Future plans are also to test other mainstream and complementary interventions. It is also recommended that the design be promoted as suitable to capture the effects of CAM interventions for other conditions. To this end I am making an oral presentation at the British Homeopathic Association Conference in October 2018.

It is recommended to work on future studies with health care assessors such as NICE. NICE have recommended that clinical research should ideally be designed, conducted, and analysed with GRADE in mind to maximize the use of research in decision making (Thornton, et al., 2013). Communication with stakeholders other than NICE, such as city councils and educationalists, initiated during this PhD, should be continued.

The importance of improving outcomes for ADHD cannot be overstated. Despite it being an 'invisible' condition, its impact is widely and deeply felt. The TwiCs design can make an important, impartial contribution in the search to improve outcomes for those with ADHD.

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Appendices

Appendix 1 Steering Committee Procedures for the STAR project.

Summary of the STAR project.

A pragmatic cohort randomised controlled trial of the clinical and cost effectiveness of treatment by homeopaths or nutritional therapists in addition to usual care, will be compared to usual care alone, for children with ADHD.

The feasibility of the cohort multiple randomised controlled trial design to assess the clinical and cost effectiveness of interventions for ADHD will be trialled.

Trial Approvals and Registration.

Independent Scientific Review has been obtained from Professor Heather Boon (University of Toronto); Dr Jack Parker (ScHARR, UoS) and Dr Val Harpin (Consultant Paediatrician, Sheffield NHS).

ScHARR research ethics approval was received 30/4/15. Reference number 003424.

University of Sheffield Research Governance sponsorship was received 10/7/15. University Research Management System (UMRS) number: 143647.

ISRCTN registration number 17723526. (http://www.isrctn.com/ISRCTN17723526)

Composition of the Steering Committee (SC).

The SC will consist of an independent Steering Committee Chair and at least two other individuals independent of the Management Team whereof at least one is a lay member and the remaining academics. The SC shall be independent and shall not be outnumbered by the Management Team members.

The Management Team is responsible for sending out invitations for SC meetings and for preparing the meeting agenda, in agreement with the SC Chair. Any SC member may put forward items for the agenda.

Personnel.

Principle Investigator: Philippa Fibert (ScHARR, UoS)

Management Team: Philippa Fibert and Dr Clare Relton (ScHARR, UoS)

Steering Committee: Prof David Daley (Nottingham University)(Chair)

Philippa Fibert (Principle Investigator)

Dr Clare Relton (Public Health, ScHARR, UoS)

Prof Mike Campbell (Medical Statistics, ScHARR, UoS)

Dr Tessa Peasgood (Health Economics and Decision Science (HEDS), ScHARR, UoS)

Dr Liz Williams (Human Nutrition, Oncology, UoS)

Catherine Witzmann (Doncaster NHS)

Gill Badby (parent representative, Sheffield NHS)

Heather Wingfield (parent representative)

Role of the Steering Committee (SC).

The Committee oversees the project. This involves ensuring that the project stays aligned with its aims and objectives; that it is carried out in line with the protocol; and that it complies with ethical, legal and safety requirements.

If necessary, the SC ensures that necessary actions are taken, such as reporting to the Sponsor (the University of Sheffield).

The SC provides advice to the Principle Investigator (PI), who is responsible for the day-to-day management, supported by the Management Team. The PI provides the SC with information on any significant changes to the protocol or any accompanying documents. Such changes must be agreed by the SC.

A sub section - the Data Monitoring and Ethics Committee (DMEC) - will be created at the first SC meeting. Its role will be to detect any potential harm to patients as early as possible. It will consider actions following any reported serious adverse events.

The DMEC will follow European Medicines Agency Guidelines (2005) www.emea.europa.eu/docs/en_GB/document_library. It will focus on ethical and safety monitoring (not data monitoring) since the trial is unblinded and adequate data monitoring can be managed by the steering committee.

Meetings of the Steering Committee.

The Steering Committee (SC) will meet a minimum of two times annually. A quorum is defined as a minimum of four SC members. Management Team member votes shall not outnumber independent members. Meetings will be chaired by the SC Chair. Any decision will be carried by a majority vote. Abstentions are not counted. The SC Chair has a casting vote. Formal minutes of SC meetings will be available to anyone by request and will be sent to the Sponsor as appropriate. SC members will be paid travel expenses for attending meetings. The Steering Committee also has the power to make decisions on a case-by-case basis via email, unless an SC member has any objections.

Appendix 2a Carer Questionnaire

ADHD QUESTIONNAIRE

Welcome to the STAR project.

Please complete this questionnaire as best as you can. It should take about 10 minutes. Try and fill in every question even if you don't remember exactly. An approximate answer is better than nothing.

When you have completed it, please put it in the freepost envelope and post it to the researchers at the University of Sheffield. Please return the questionnaire as soon as you can.

Your answers will help us understand how to make life easier for children and their families with ADHD.

Child's name.....Age……..

Your relationship to the child.....

Please tick a box on each line that best describes your child

	NOT AT ALL TRUE (never, seldom)	*JUST A LITTLE TRUE (occasionally)*	*PRETTY MUCH TRUE (often, quite a bit)*	*VERY MUCH TRUE (very often, very frequently)*
Temper outbursts; explosive, unpredictable behaviour				
Excitable, impulsive				
Restless or overactive				
Cries often and easily				
Inattentive, easily distracted				
Fidgeting				
Disturbs other children				
Demands must be met immediately – easily frustrated				
Fails to finish things he/she starts				
Mood changes quickly and drastically				

Your child's health

Please tell us about all your child's diagnoses, e.g. autism spectrum, conduct, oppositional or learning disorder, anxiety or depression, Tourette's, asthma etc

Diagnosis	*Any medication taken*
ADHD	
Other (name)	
Other (name)	
Other (name)	

In the last 6 months, how often have you been visited/ visited the following about your child?

	Number of visits
Doctor	
Hospital	
Social worker	
Police	
Other (please describe)	

What else have you used to help your child?

	In the past	*Now*
Family Action parenting course	yes ☐ no ☐	yes ☐ no ☐
Other parenting class	yes ☐ no ☐	yes ☐ no ☐
Sessions with a psychologist	yes ☐ no ☐	yes ☐ no ☐
homeopathy	yes ☐ no ☐	yes ☐ no ☐
Other (name) ……..	yes ☐ no ☐	yes ☐ no ☐
Other (name) ……..	yes ☐ no ☐	yes ☐ no ☐

The next questions ask about how your child is today. For each question, read all the choices and decide which one is most like your child today

Then put a tick in the box next to it like this ☑. Only tick **one** box for each question.

Example: Today my child feels quite upset so I will tick this box.

Upset

☐ My child does not feel upset today

☐ My child feels a little bit upset today

☐ My child feels a bit upset today

☑ My child feels quite upset today

☐ My child feels very upset today

1. Worried

☐ My child does not feel worried today

☐ My child feels a little bit worried today

☐ My child feels a bit worried today

☐ My child feels quite worried today

☐ My child feels very worried today

2. Sad

☐ My child does not feel sad today

☐ My child feels a little bit sad today

☐ My child feels a bit sad today

☐ My child feels quite sad today

☐ My child feels very sad today

3. Pain

☐ My child does not have any pain today

☐ My child has a little bit of pain today

☐ My child has a bit of pain today

☐ My child has quite a lot of pain today

☐ My child has a lot of pain today

4. Tired

☐ My child does not feel tired today

☐ My child feels a little bit tired today

☐ My child feels a bit tired today

☐ My child feels quite tired today

☐ My child feels very tired today

5. Annoyed

☐ My child does not feel annoyed today

- ☐ My child feels a little bit annoyed today
- ☐ My child feels a bit annoyed today
- ☐ My child feels quite annoyed today
- ☐ My child feels very annoyed today

6. School Work/Homework (such as reading, writing, doing lessons)

- ☐ My child has no problems with their schoolwork/homework today
- ☐ My child has a few problems with their schoolwork/homework today
- ☐ My child has some problems with their schoolwork/homework today
- ☐ My child has many problems with their schoolwork/homework today
- ☐ My child can't do their schoolwork/homework today

7. Sleep

- ☐ Last night my child had no problems sleeping
- ☐ Last night my child had a few problems sleeping
- ☐ Last night my child had some problems sleeping
- ☐ Last night my child had many problems sleeping
- ☐ Last night my child couldn't sleep at all

8. Daily routine (things like eating, having a bath/shower, getting dressed)

- ☐ My child has no problems with their daily routine today
- ☐ My child has a few problems with their daily routine today
- ☐ My child has some problems with their daily routine today
- ☐ My child has many problems with their daily routine today
- ☐ My child can't do their daily routine today

9. Able to join in activities (things like playing out with their friends, doing sports, joining in things)

- ☐ My child can join in with any activities today
- ☐ My child can join in with most activities today
- ☐ My child can join in with some activities today
- ☐ My child can join in with a few activities today
- ☐ My child can join in with no activities today

(©University of Sheffield)

Please use this space if there's anything else you'd like to tell us about your child

Thank you very much for completing this questionnaire. We just need a bit more information, and confirmation that you and your child are happy to continue being part of the STAR project.

Are you happy for us to contact you again: yes ☐ no ☐

Signature……Date……

Child's date of birth ……

Contact details:

Address:……

Phone number……

Email……

We would like to ask a teacher of your child to fill in a questionnaire as well. May we contact your child's school? yes ☐ no ☐

School name……..

Can you suggest the name of a teacher who knows your child well?

.....

Date of child's ADHD diagnosis.....

Which doctor gave the diagnosis? ……

Where they were diagnosed? (e.g Ryegate children's centre, CAMHS, etc)
……

Please post this as soon as possible in the accompanying freepost envelope, or send it to Philippa Fibert, Sheffield School of Health and Related Research, Regent Court, 30 Regent Street, Sheffield, S1 4DA.

Appendix 2b Teacher Questionnaire

I understand that you work with ……..

Thank you so much for your help with this project. Your information is a very important component of our research.

Please complete the questions below as best you can. Approximate answers are better than nothing. Then return it in the accompanying FREEPOST envelope; or send it to Philippa Fibert, Sheffield School of Health and Related Research, Regent Court, 30 Regent Street, Sheffield, S1 4DA; or email it to p.fibert@sheffield.ac.uk

Your name……..……

Your relationship to the child (e.g class teacher, classroom assistant, head teacher)

……..

School name……

Educational year of the child……

How disruptive has this child been in the classroom during the last 2 weeks (please circle)

(As good as it gets) 0…….1……..…2……..…3……..4……5 (as bad as it gets)

How many days off school has this child had in the last 6 months? ☐☐

Has this child been excluded from school over the last 6 months?

yes ☐ no ☐ If yes, number of days ☐☐

1. **Does this child have a teaching assistant? yes ☐ no ☐ If yes, how many hours a week? ☐☐**

2. **Does this child have other help in school for their ADHD? yes ☐ no ☐**

If yes, please describe it, and how often they have it

……

ADHD diagnosis. *Please tick a box on each line that best describes this child*

	NOT AT ALL TRUE *(never, seldom)*	*JUST A LITTLE TRUE* *(occasionally)*	*PRETTY MUCH TRUE* *(often, quite a bit)*	*VERY MUCH TRUE* *(very often, very frequently)*
Temper outbursts; explosive, unpredictable behaviour				
Excitable, impulsive				
Restless or overactive				
Cries often and easily				
Inattentive, easily distracted				
Fidgeting				
Disturbs other children				
Demands must be met immediately – easily frustrated				
Fails to finish things he/she starts				
Mood changes quickly and drastically				

	NOT AT ALL	*JUST A LITTLE*	*QUITE A BIT*	*VERY MUCH*
Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities				
Often has difficulty sustaining attention in tasks or play activities				
Often does not seem to listen when spoken to directly				
Often does not follow through on instructions and fails to finish schoolwork, chores, or duties				
Often has difficulty organizing tasks and activities				
Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework)				
Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)				
Often is distracted by extraneous stimuli				
Often is forgetful in daily activities				
Often fidgets with hands or feet or squirms in seat				
Often leaves seat in classroom or in other situations in which remaining seated is expected				
Often runs about or climbs excessively in situations in which it is inappropriate				
Often has difficulty playing or engaging in leisure activities quietly				
Often is "on the go" or often acts as if "driven by a motor"				
Often talks excessively				
Often blurts out answers before questions have been completed				
Often has difficulty awaiting turn				
Often interrupts or intrudes on others (e.g., butts into conversations/games)				

Appendix 3. Therapists Consultation form.

STAR Therapist Form

Please complete this questionnaire at the end of each consultation. You can either leave it at Wellforce Reception; email it to p.fibert@sheffield.ac.uk; or send it to Philippa Fibert, The Coppins, Horsleys Green, High Wycombe, Bucks HP14 3UX

Your Name……Date……

Patient name……..

Consultation date……Consultation venue ……..

Prescription. (name, potency, frequency)…….
……

Did your patient take the remedy as suggested by you? y/n. If no, please describe what they did.
……
……

Did your patient have a homeopathic aggravation/adverse event not related to your treatment? y/n. Please describe if yes (and fill in the Adverse event form)……..
……
……
……

Anything else important you were told at this consultation (e.g they were in trouble with the law; did well at school; a non-ADHD sx improved etc)……
……
……

Appendix 4. Flyer

Does your child have ADHD?

Researchers at the University of Sheffield are studying ADHD, and testing some treatments to see how helpful they are in relieving symptoms and improving long-term outcomes.

We are looking for as many families as possible to take part, from all over the UK. So please get in touch. To do so, go to:

www.starsheffield.com

Or contact **Philippa:** 07543345046, p.fibert@sheffield.ac.uk

www.facebook.com/starsheffieldADHD

The School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent St, Sheffield.

The University Of Sheffield.

Appendix 5. Letter to Headteachers

Dear …….,

A child from your school is participating in research we are conducting at the University of Sheffield observing children with ADHD. Our aim is to improve understanding and test novel interventions to see if they make life easier for all stakeholders.

We would appreciate your input particularly as ADHD has such an impact in school. Please could you ask the member of staff who spends most time with**……**, age ….., suggested by her carer to be……..**,** to complete the enclosed questionnaire and return it as soon as possible in the attached Freepost envelope. Alternately the questionnaire can be completed on line by visiting www.starsheffield.com.

We will be sending out a similar questionnaire in 6 months' time. We will ring you in the near future to give you the opportunity to ask any questions about the project and check how her teacher would prefer to be contacted next time (post, email or telephone).

Carers have given their consent for this information to be given and all the information that you give us will be anonymous and treated as confidential.

I have enclosed a project flyer in case there are any other children in your school with diagnoses of ADHD who you think might be happy to participate in the project. We are trying to contact as many families as possible. We will keep you updated about our findings. Please feel free to contact me meanwhile for any further information.

Many thanks in advance for your assistance.

Yours, Philippa Fibert

Sheffield School of Health and Related Research, Regent Court, 30 Regent Street,

Sheffield, S1 4DA.

Mobile 07543345046

p.fibert@sheffield.ac.uk

Appendix 6. Invitation to Treatment letters.

Dear ……

Thank you for recently completing and returning the STAR Questionnaire. Your child is one of 38 who have been chosen to try a course of **homeopathic treatment** for their ADHD. You are being offered the opportunity for your child to receive free treatment for up to one year so researchers at the University of Sheffield can investigate whether homeopathic treatment provides some extra help for your child's ADHD.

What is homeopathic treatment?

Homeopathy is considered to be a gentle, safe, natural form of healing where the body is stimulated to heal itself. More information about homeopathy can be found at www.homeopathy-soh.org/about-homeopathy.

Homeopathic treatment focusses on the individual, not the diagnosis: the things that are unique and different about your child not their common ADHD symptoms. We are interested in whether homeopathic treatment provides any extra help. Homeopathic remedies should not interact with any medications your child is currently taking, and you should continue to take any medications provided by your doctor and keep up your usual contact with them.

What will my child's homeopathic treatment consist of?

In homeopathy the individual symptoms of your child are matched with an appropriate homeopathic medicine (known as a remedy), which is believed to trigger self-healing. To find the most appropriate remedy for your child, you will meet with a professionally trained homeopath who will ask all about your child and their unique symptoms. Homeopathic treatment is a process, and remedies will be reviewed and modified at follow up consultations according to your child's needs and the improvements they make.

You and your child will be offered a series of up to 8 consultations with a homeopath during one year, and appropriate homeopathic remedies to take in-between.

Who is organising the research?

This study is being carried out at the University of Sheffield School of Health and Related Research, by Philippa Fibert

Will the information I give be kept private?

Yes. All information you provide will be kept strictly confidential. Once we have collected the information, all the data will be made anonymous and your child will not be identifiable.

What do I do now?

Please ask your child if they are happy to participate. Once everyone is happy, you can let us know. Or Philippa will be ringing you to answer any questions you may have, and you can let her know then. With your permission, she will then give your details to a homeopath who will ring you to arrange to meet.

I am happy to take part in the STAR Project. I agree to attend consultations approximately every 6 weeks, and take the homeopathic remedies prescribed by my homeopath, or inform them if I can't.

I understand that I may stop participation at any time I wish to.

Child's name……

Child's signature……

Adult's name……

Adult's signature……..……

You can let us know if you'd like to take up this offer by returning this page in the FREE envelope provided; texting 07543345046; or emailing Philippa p.fibert@sheffield.ac.uk

Dear ……

Thank you for recently completing and returning the STAR Questionnaire. Your child is one of 38 who have been chosen to try a course of **nutritional therapy** for their ADHD. You are being offered the opportunity for your child to receive free treatment for up to one year so researchers at the University of Sheffield can investigate whether nutritional treatment might help ADHD and can learn more about your child's experience with such treatment.

What is nutritional therapy?

Nutritional therapy is individually tailored supplements, information, and advice about nutrition to help ADHD. This means you might be given some supplements considered helpful for ADHD, some information about foods which might be aggravating your child's ADHD, and an individually tailored plan with some menu suggestions.

What will my child's nutritional treatment consist of?

You and your child will be offered a series of up to 8 consultations with a nutritional therapist. They will discuss a range of options shown to be helpful for ADHD, and devise a plan together with you. Your nutritional therapist will then provide an individually tailored summary sheet, recipe ideas and/or supplements. These will be reviewed and modified at follow up consultations. You can continue to take any medication or treatment provided by your GP or other health practitioners and should keep up your usual contact with them.

Who is organising the research?

This study is being carried out at the University of Sheffield School of Health and Related Research, by Philippa Fibert.

Will the information I give be kept private?

Yes. All information you provide will be kept strictly confidential. Once we have collected the information, all the data will be made anonymous and your child will not be identifiable.

What do I do now?

Please ask your child if they are happy to participate. Once everyone is happy, sign and return the consent form at the end of this letter, or contact Philippa by email or text (details below).

What happens next?

Philippa will ring you to answer any questions. With your permission, she will then give your details to a nutritional therapist who will ring you to arrange to meet.

I am happy to take part in the STAR Project. I agree to attend consultations with a nutritional therapist, or inform them if I can't.

I understand that I may stop participation at any time I wish to.

Child's name…… Child's signature…….

Adult's name…… Adult's signature…….

To let us know you'd like to take up this offer, either return this page in the FREE envelope provided; text 07543345046; or email Philippa p.fibert@sheffield.ac.uk

Appendix 7. Letter to GPs

School of Health and Related Research (ScHARR), University of Sheffield,

Regent Court, 30 Regent Street,

Sheffield.

Dear…….

I am a researcher in the field of ADHD at the School of Health and Related Research, University of Sheffield.

This letter is to let you know that we are conducting a clinical trial exploring the effectiveness of two complementary treatments for ADHD. The trial is to investigate whether the treatments might help children aged 5-18 with ADHD, and learn more about their experience with such treatment.

The treatments we are trialling are treatment by nutritional therapists, and treatment by homeopaths, and these are being compared to treatment as usual to explore whether the therapies provide any extra help.

The treatments are adjunctive to what they are currently doing, and participants are advised to continue with all their prescribed medication and maintain their usual contact with you. The treatments are considered to be safe and non-invasive, and no known interaction with conventional medication or side effects has been observed. Families are recruited through non NHS charities and support groups.

The study has been ethically approved under the University of Sheffield's Ethics Review Procedure. As a health care research study, the project also underwent the University's health care research governance procedure in line with the Department of Health's Research Governance Framework, including appointing the University as the Research Governance Sponsor and ensuring all relevant approvals were in place. The project was additionally risk assessed under the University's quality assurance procedure for human intervention studies, and confirmed to be low risk.

Please contact us should you like any further information about the study.

Yours Philippa Fibert (Principle Investigator, The STAR project)

Appendix 8. Adverse event guidelines.

Introduction

This document has been developed for the STAR project, and its first trial: comparing the clinical and cost effectiveness of treatment of ADHD by homeopaths and nutritional therapists with treatment as usual, being run at the School of Health and Related Research (ScHARR), University of Sheffield.

The aim is to assess the acceptability and comparative clinical and cost effectiveness of adjunctive treatment provided by homeopaths and nutritional therapists in addition to usual care for children with ADHD. A random selection of children recruited to an ADHD cohort will be offered treatment by homeopaths or treatment by nutritional therapists and their outcomes will be measured every 6 months.

It is an important aspect of this trial that any adverse events are reported to the research management team to ascertain the safety of the interventions, and ensure best care of participants. Therapists must check for any adverse events each time they meet with families. Carers may also report adverse events directly to the research management team. They are informed of this when they are first offered a treatment.

The Adverse Event (AE) guidelines below are based on: the Common Terminology Criteria for Adverse Events (CTCAE) (U.S. Department of Health and Human Services 2010); European Commission Guidelines (2011); the Standard Operating Procedure developed by the Clinical Trials Research Unit (CTRU) at the University of Sheffield (2012); STAR trial protocol; and existing homeopathy literature.

What is an adverse event?

Many definitions exist. The CTCAE guidelines will be used which define an adverse event (AE) as: "… any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with

the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure."

Different grades of adverse events

Adverse events may be categorised in various ways. The CTCAE guidelines use 5 categories:

Grade 1: Adverse Event. Mild or asymptomatic or mild symptoms. Clinical or diagnostic observations only.

Intervention not indicated.

Grade 2: Adverse Event. Moderate or minimal or limiting age-appropriate instrumental activities of daily living (ADL) (Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Local or non-invasive intervention indicated.

Grade 3: Serious Adverse Event. Severe or medically significant but not immediately life-threatening. Resulting in significant disability or incapacity. Limiting self-care ADL (Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). Congenital anomaly or birth defect. Events that may require intervention to prevent any of the mentioned consequences.

Hospitalisation or prolongation of hospitalisation indicated

Grade 4: Serious Adverse Event. Life-threatening consequences. This refers to events where the subject was at risk of death, not where the event hypothetically could have caused death.

Urgent intervention indicated

Grade 5: Serious Adverse Event. Death related to Adverse Event.

Urgent intervention indicated

Adverse events in homeopathy and homeopathic aggravations

Homeopathic remedies are considered to be safe (Bornhöft et al. 2006). They do not represent a risk of toxicological effects or interactions with conventional drugs (Woodward 2005). Nevertheless some adverse events have been reported by various authors (e.g. Dantas & Rampes 2000, Grabia & Ernst 2003, Haidvogl et al. 2007). These have been characterised as transient and mild (Dantas & Rampes 2000) or mild to moderate (Grabia & Ernst 2003).

No serious adverse events have been reported (ECCH 2009). The adverse events most commonly reported include: headaches, tiredness, skin eruptions, dizziness, diarrhoea or loose stools, and aggravations of patients' pre-existing symptoms (Dantas & Rampes (2000).

Mild and transient aggravations of patients' pre-existing symptoms, usually associated with increased feelings of wellbeing, are commonly referred to as 'homeopathic aggravations' in the homeopathy literature. They occur relatively soon after taking a homeopathic medicine and are normally considered favourable and part of patients' curative process (Endrizzi et al. 2005, Thompson et al. 2004). Such aggravations occur more commonly with a particular homeopathic protocol to be used in this trial (CEASE, Smits, 2010).

What should therapists in the STAR project do?

Therapists should check for adverse events at each consultation. They should note and complete the adverse event form for any adverse event (including homeopathic aggravations). They should immediately report anything considered to be a serious adverse reaction: i.e at least the grade 3 criteria as defined in the CTCAE guidelines. This would include:

- any severe or medically significant reaction, even though they may not be life-threatening
- reactions resulting in hospitalisation or prolongation of hospitalisation
- reactions limiting patients ability for self-care, including daily living activities such as bathing, dressing and undressing, feeding themselves, using the toilet, taking medications

When in doubt, therapists should contact the management team (see emails below) who will determine what should be done and whether the event requires reporting to the Data Monitoring and Ethics committee (DMEC).

The form should be completed within 24 hours of the event and should be emailed to the STAR management team: either the Chief Investigator, Philippa Fibert at p.fibert@sheffield.ac.uk or Dr Clare Relton at c.relton@sheffield.ac.uk

What should the STAR Management Team do?

When the Management Team receives reports of adverse events from therapists and/or patients, they will report serious events to the STAR Data monitoring and ethics committee (DMEC) within 24 hours.

The DMEC will then report the SAE as deemed appropriate to the Head of the School of Health and Related Research (ScHARR); the sponsor (University of Sheffield); the STAR Steering Committee; the patient's family and/or their GP.

The Management Team will complete the University of Sheffield Adverse Event Report Form in line with the Standard Operating Procedure developed by the Clinical Trials Research Unit (CTRU) at the University of Sheffield (2012).

They will report: their assessment of the seriousness, frequency and intensity of the Adverse Event; concomitant treatment; the assessed relationship to the therapist's treatment; any actions taken and the outcome. When in doubt, the Management Team will discuss the issue with the DMEC.

1. **Seriousness**: Death; life threatening; inpatient hospitalisation; prolonged hospitalisation; persistent or significant disability/incapacity; congenital abnormality/birth defect.
2. **Frequency**: Isolated; intermittent; continuous; unknown.
3. **Intensity**: Mild; moderate; severe.
4. **Concomitant treatment**: Any treatment other than the treatment provided by the homeopath.
5. **Assessed relationship to therapist's treatment**: Definite; probable; possible; unlikely; unrelated; not assessable.

6. **Action taken**: None; reduce dose; treatment withdrawn; specific treatment; other.
7. **Outcome**: Recovered; improved; unchanged; deterioration; persisted; death.

Appendix 9. Adverse event form

An adverse event includes, but is broader than, unintended errors and mistakes arising from research activity, resulting in one or more research participants having symptoms or being caused physical or psychological harm or serious distress. Refer to the STAR Adverse Events Guidelines for clarification.

Please complete this form within 24 hours of the event occurring and email it to Chief Investigator Philippa Fibert p.fibert@sheffield.ac.uk and/or ring her on 07543345046.

Date:
Therapist's name:
Patient's name, date of birth and contact details:
Patient's GP name and contact details:
Details: When did the event take place and for how long? What happened and what was the impact? Any thoughts on why it occurred:
Action taken:
Any action or planned action to limit the risk of the event re-occurring?

Appendix 10. Risk Guidelines for therapists treating children with ADHD

Introduction.

This document has been developed for homeopaths and nutritional therapists interacting with families included in the pragmatic cohort randomized controlled trial of the clinical and cost effectiveness of treatment of ADHD (STAR) project at the School of Health and Related Research (ScHARR), University of Sheffield.

The policy is derived from: '*A guide to inter-agency working to safeguard and promote the welfare of children'*; '*Information Sharing*: *Advice for practitioners providing safeguarding services to children, young people, carers and carers'*. (Department for Education, March, 2015); and www.safeguardingsheffieldchildren.org.uk (local safeguarding children board).

Clinical risk is the possibility of something negative happening as a direct result of the behaviour of a patient or people in their surroundings. ADHD families are considered a vulnerable population, with more prevalent risk factors (Biederman, 2002) and the symptoms of ADHD and abuse can overlap. This document covers information about: the context; recognising signs and symptoms of abuse; what to do if there are concerns about the child or family; how to manage those concerns; recording and managing confidential information.

Training in child protection policy is considered imperative for this study, and all therapists will complete the 'awareness of child abuse and neglect' emodule: (www.safeguardingsheffieldchildren.org.uk), which trains therapists to recognise the signs of, and respond correctly to physical, sexual, emotional abuse and neglect.

This policy document recognises that effective safeguarding systems are those where the child's needs are paramount, and the needs and wishes of each child are put first. Therapists need to be alert to any risks of harm that individual abusers, or potential abusers, may pose to children; know how to share appropriate information in a timely way; and use their judgement to put the child's needs at the heart of safeguarding.

Confidentiality

- Confidentiality between therapists and families should be maintained at all times, UNLESS the therapist deems that the risk of abuse is great enough to require activating statutory safeguarding procedures.
- Therapists should only make a decision to breach confidentiality after discussion with the Principle Investigator of the project.

Competency

- Therapists should work within the limits of their competency and seek advice/supervision when they feel outside those limits
- They should work according to the code of ethics developed by their professional organisation
- They should attend the regular supervision provided for the trial, and individual supervision dependent on need and experience

What is abuse?

This is covered more fully in the emodule accessible at www.safeguardingsheffieldchildren.org.uk.

The definition of abuse is 'a form of maltreatment of a child by inflicting harm, or by failing to act to prevent harm'. It can be Sexual, Physical, Emotional, or due to Neglect. Children may be abused in a family, in an institutional or community setting, by those known to them, or by others (e.g. via the internet). They may be abused by an adult or adults, or another child or children.

Several of the signposts for abuse are common ADHD symptoms. You will need to consider these very carefully and use your professional judgement and try to understand what might be behind the symptoms. For example is lack of eye contact between carer and child a symptom of ASD spectrum or a sign of neglect? Is poor educational achievement due to innate concentration difficulties or abuse etc. Ask yourself what is provoking the behaviour? You also need to consider that ADHD may possibly manifest as a response to abuse. You therefore need to be aware of the signs and symptoms, and what to do in the unlikely circumstance that you suspect abuse.

ADHD children can be exasperating and drive carers to their limits. Discipline may appear extremely harsh verging on abusive. Be compassionate in your understanding of the carers attempts to manage their child's behaviour and considerate that the carers may also have ADHD, but aware where parental response seems extremely disproportionate.

The four identified types of abuse are defined below:

1. Sexual. This involves forcing or enticing the child to be involved in sexual activity, whether or not they are aware of it. It may be physical, or just making them watch. This is very difficult to diagnose, and should only be suspected it the child actually says something.
   Signposts are: loss of concentration, enuresis, soiling, poor performance at school, self-harm, and inappropriate sexualised behaviour.

2. Physical. Hitting, shaking, poisoning, burning, drowning, suffocating, carers fabricating symptoms or deliberately inducing symptoms. Smacking is not illegal, but if it causes bruising, swelling, cuts, grazes or scratches it is, and liable to 5 years imprisonment.
   If you are concerned about the injury: 1. Ask the child how it happened. 2. Ask the carer how it happened. Note the exact words. Be concerned if the child isn't allowed to tell you; the story seems inconsistent, medical help wasn't sought when you think it should have been; or carers appear hostile. However, consider that the child's carers may have ADHD, and expect hostile responses and defensive reactions.
   A series of marks may indicate repeated injury. Consider the positioning of the bruising, how well it matches the story and how easy it might be to obtain accidentally. Eg two bruised eyes or bruising of the outer ear may be difficult to obtain accidentally.
   If you suspect a fracture, ensure families seek medical help. Never undress a child for examination without consent from carer/carer and child and in the presence of carer/carer.
3. Emotional. This is defined as 'Persistent emotional maltreatment conveying to the child that they are worthless, unloved or inadequate'. Consider that ADHD carers may have received this kind of modelling themselves and therefore use it on their children. Signposts include: head banging or other forms of self stimulation; hyperactivity, reduced attention span, developmental delay, aggression at school, low self esteem, self harm.
4. Neglect is defined as 'persistent failure to meet a child's physical and emotional needs, likely to result in serious impairment of health and development'.
   This can be failure to provide adequate clothing, food or shelter; protect the child from physical or emotional danger and harm; ensure adequate supervision and medical treatment.
   There are degrees of neglect. Be careful about imposing your own standards.
   Signposts are: developmental problems, recurrent minor infections, poor educational performance, language delay, failure to thrive, conduct disorders, indiscriminate attachment to strangers, lack of eye contact

Notifiable incidents

Local authorities have a duty to make enquiries under section 47 of the Children Act 1989 if they have reasonable cause to suspect that a child is suffering, or is likely to suffer, significant harm, to enable them to decide whether they should take any action to safeguard and promote the child's welfare. There may be a need for immediate protection whilst the assessment is carried out.

A notifiable incident requires immediate notification to safeguarding authorities and includes:

- death of a child (including cases of suspected suicide), whether or not abuse or neglect is known or suspected.

- a child has been seriously harmed and abuse or neglect is known or suspected

Monitoring and measuring the level of risk

When you first suspect potential risk of abuse:

- Explore this directly with the family using every day language, open questions (who, when, what, how) not leading, closed questions.
- Record exactly what they have said. Record in detail why you suspect the abuse and your observations using the project risk assessment form. Record any actions taken with dates and times.
- Share your anonymised concerns immediately with the PI and/or your supervisor.

Procedures to manage identified risk of abuse

If you, the PI, and/or your supervisor are in agreement that the child is at serious risk of abuse in their current circumstances, you have a statutory duty to report the perceived risk. Please consider the following:

- If the child has disclosed that they have suffered abuse to you, be aware that this has been extremely hard for them and means they trust you. You will need to tell them that you need to pass on to other people what they have told you because they or other children may be hurt. Whilst your primary concern is always the wellbeing of the child, you have a duty to refer child protection concerns. Similarly, if the child's carer chooses to disclose that they or their child has suffered from abuse, you will similarly need to make them aware if you need to pass this information on.
- Ask the family if they are already under supervision by social services, who their care worker is, and tell them that you will be contacting them. Reassure them at all times that this is with the best interests of the child.

Actions

For non-urgent concerns, discuss with PI and/or your supervisor.

For urgent concerns, contact the PI immediately (07543345046). If she is unavailable contact Dr Clare Relton (0114 2220796/07879872892).

If neither are available, ring the free Sheffield safeguarding advisory desk helpline for advice (Monday to Friday, 9 until 5 pm) 0114 2053535. Out of hours, ring emergency service 0114 2734855

The PI and Dr Relton will bring any urgent concerns to the Data monitoring and Ethics Committee (DMEC) within 24 hours of being alerted to the concern.

Appendix: SOH code of conduct.

64. Avoid physical examination unless in the presence of the carer and with the child's permission

78. Avoid disclosing any information about patients….and preserve confidentiality at all times, unless clear and ethical or legal concerns overrule this

80. The following legal and moral exceptions may justify information being given to third parties. a) in an emergency or other dangerous situation where in the opinion of the therapist, the information may assist in the prevention of possible injury to the patient or another person. b) when required to do so by rule of law. By virtue of employment in an organoisation operating local protocols, eg under the Children's Act 1989.

Appendix B. We are legally required to take action in any case where we suspect a child is at risk through mental, emotional, physical abuse or neglect (Barkley & Fischer, 2010)

Appendix 11. Description of homeopathy ADHD research studies

Studies excluded from the systematic review on screening, with reasoning.

Study	*Reason for exclusion*
Lottering	Unpublished MSc thesis of a complex formula 'Quietude'
Smith 2001	Unpublished MSc thesis of complex formulas cerbo and nerva
Cockcroft	Unpublished MSc thesis of the single remedy phosphorous
Barnard 2010	Unpublished MSc thesis: uncontrolled case series.
Goetz 2012	This RCT was found not to include homeopathy on full reading
Mc Clean and Garland 2005	Unpublished observational study of children in danger of exclusion (not necessarily with an ADHD diagnosis)

Studies included in the literature review

Lamont 1997

A quasi-randomised controlled trial with partial cross-over (alternate allocation) of 43 children with ADHD confirmed by psychological testing, mean age of 10years, of which 6 were already taking stimulant medication but still displayed symptoms. All children were in foster homes, in care or under the supervision of a social worker. Individualised homeopathic remedies were prescribed for each child following a consultation using classical homeopathic prescribing. This was the only contact between child and homeopathic physician. Medicines were given as 6 x 200c pills daily for up to 5 days. Progress was followed-up every 10 days by phone with carers or carers with the option of changing the medicine on two further occasions. The placebo group received an indistinguishable placebo pill. Later they were crossed-over to receive verum homeopathy as described above.

Outcomes were reported by carer to the researcher by telephone 10 days after each prescription using an un validated five-point rating scale of "change in hyperactivity" which spanned -2 'much worse' to 0 'no change' to +2 'much better'. Explanation for the use of this measure was justified by the author, who explained that a pilot study had found a halo effect 'eliminating the utility of most items' and that carers were better able to understand and respond to the simple scale.

Strauss 2000

An RCT (no details of randomisation) of 20 children with previously diagnosed ADHD (no confirmation) aged between 7-10 years of which half (equally distributed) were already tak-

ing stimulant medication.. A complex formula homeopathic medicine was used containing selenium in 10X, 15X, 30X, 200X and potassium phosphate in 2X, 10X, 30X, 200X (sold commercially in South Africa to improve concentration, memory and alertness). Ten drops were taken three times daily. The placebo group received an identical liquid solution with the same instructions. Drops were taken for two months.

Outcomes were measured at baseline, 30 days and 60 days using The Conners' Rating Scales (CRS); and a child performance task termed the Childrens' Checking Task to assess sustained attention.

Frei 2001

This open label study evaluated 115 children (mean age 8.3) at diagnosis of ADD/ADHD by the consultant paediatrician, who ran a conventional practice which provided homeopathic treatment. The children were first treated with individualised homeopathic remedies. Children who did not improve sufficiently (50% improvement in CGI) were changed to Ritalin. After an average treatment time of 3.5 months, 75% (N=86) children attained an improvement rating of 73% with homeopathic remedies. 22% (N=25) children subsequently treated with Ritalin attained an improvement rating of 65%. 3 children didn't respond to either treatment and 1 left the study.

Frei 2005

From the research above (Frei, 2001) it had been found that gains whilst taking remedies were only maintained whilst continuing to take them, allowing a controlled comparison of deterioration in symptoms under placebo and maintenance of improvement under verum.

A screening phase identified responders who successfully responded to homeopathy by demonstrating at least a 50% reduction in their ADHD symptoms. 83 children with ADHD confirmed by neuropsychological examination entered the screening phase. Individualised homeopathic remedies were prescribed as daily liquid doses (LM potencies) according to Bönninghausen's methodology which is somewhat used on the continent, but not in the UK. Children were seen only once by the homeopathic physician with treatment progress assessed by carers at 4-weekly intervals and remedy adjusted as necessary. All other medication or treatments for ADHD had to be stopped for the duration of the screening and the trial.

62 children (mean 10 yrs) entered the RCT phase when their symptoms had improved by 50% under homeopathic treatment. In the trial phase participants received either the successful remedy (n=31) or an identical placebo (n=31) to be taken daily for 6 weeks followed

by cross-over. No contact with the homeopathic physician occurred during the cross-over trial phase.

Outcomes. Screening stage: CPRS-R Carer and Teacher forms, Kinsbourne Attention Questionnaire. Baseline: CGI-P, Questionnaire of Change of Behaviour (QCB), VLMT (auditory learning test), WISC (Wechsler intelligence test),K-ABC Kaufman Assessment Battery for Children, TAP Test Assessment battery for Attention Performance. Final outcomes: CGI-Carer, VLMT, QCB, WISC.

Jacobs 2005

An RCT (computer generated, blocked, stratified algorithm) of 43 children with confirmed ADHD diagnosis, mean age of 9 years. 9 participants were already taking stimulant medication (n=5 active, n=4 placebo).

Individualised homeopathic remedies were prescribed using the Sankaran method with option to vary prescription at 6 and 12 week follow-up. 21 children received a single remedy and 22 children received an indistinguishable placebo. The trial lasted for 18 weeks in total.

Outcomes Baseline: CPRS, CGI-P(Carer), CGI-T (teacher), Continuous Performance Test (CPT). Follow-up at 18 weeks: CPRS, CGI-P, CGI-T, CPT, Stimulant Side Effects Checklist, Clinical Global Impression (Clinicians)

Barvalia 2011.

This was a nonrandomized, within subjects pre and post-intervention study of sixty autistic children of both sexes, ≤12 years. Autism was measured using the ATEC, and ADHD symptoms using the Autistic Hyperactivity Scale. Children were observed for the initial 6 months (control period) and the same children were then treated for 1 year.

Razlog 2012

An RCT (no details of randomisation) of 30 children aged 5-11 pre-diagnosed with ADHD and not taking medication. A non-individualised remedy considered to be indicated for symptoms such as impatience, irritability and inattention was given in two different potencies. Group 1 took mother tincture Valeriana officinalis; group 2 took low homeopathic potency Valeriana officinalis 3X; and group 3 took a placebo consisting of an identical liquid solution. All groups took 10 drops, three times a day after meals, for two weeks.

Outcomes: Barkley and DuPaul teacher rating scale, the children's checking task (CCT), and CPRS measured at baseline, week one, week two and week three.

Brule 2012

An open label pilot study with no comparator, of 30 children (mean age 9.5) with a diagnosis of ADHD by clinical psychiatrist. Children received homeopathic treatment of 10 consultations and individually prescribed homeopathic remedies) from two homeopaths. Children on regular stimulant medication were included.

Outcomes were measured at baseline and at each of the 10 appointments using CGI-P and Measure your Own Medical Outcome Profile (MYMOP) which asks for selection of two most bothersome symptoms; an activity influenced by the condition; and wellbeing; and measures them on a likert scale of 0-6.

Oberai 2013

An RCT of 61 children (mean age 9.3) on no other medications, with ADHD confirmed by psychiatrist. Children were randomly assigned to receive individualised homeopathic remedies or an identical placebo, daily for one year.Remedies could be changed every 3 months. Consultations are not described.

Outcomes: CPRS-R; CGI-SS; CGI-IS at baseline and every month up to one year. Academic performance recorded at baseline and one year.

Fibert 2016

An open label comparative consecutive case series of 30 children with a prior diagnosis of ADHD. 20 children who received individualised homeopathic treatment for one year (visits every 6 weeks + I-HMPs), were compared with 10 children enrolled subsequently, who received similar time and attention from the same practitioner for 4 months.

Comparative outcomes were measured at baseline and after 4 months and long-term outcomes of treated children were measured after one year using DSMIV characteristics (CPRS-R-L) and MYMOP. Via MYMOP symptom choices it was found that 20/30 participant's carers considered anger to be the issue that was most bothersome

Appendix 12. Lost Voices

[Nathan enters stage, puts glass of water on small table and addresses the audience]

I guess from a humanistic perspective,

we often fear what we don't understand.

Keep at arms length things that don't make sense,

daily, bombarded by 1000s of messages, advert and influences

- our minds are in high demand.

So whether we like it or not, we all stereotype,

we create snap judgements in the blink of an eye

based upon a wealth of experience across the span of our lives.

I'd hate to admit I'd judge a book by the exterior of it

- but if i said, I'd read every book I'd ever picked up, that'd be a lie.

Now we've all had a requirement to fill a desire. Then

found it difficult before the age of retirement.

Imagine wanting what you cant have, because you have what you didn't want,

knowing the message to write, but not being able to choose the font.

So I guess this is the part where I should introduce me;

they call me attention deficit hyperactivity disorder, ADHD

and we know the difference between knowing and KNOWING.

So I've been invited here to explain a little more about me.

[enter Dan, puts wallet on table next to glass of water and looks at Nathan]

Imagine talking to your mate

and everything he says is great,

you like his idea and energy,

of course you concentrate.

Then you notice something strange, [piano starts]

your eyes drift the other way.

The piece of paper becomes louder

than everything he has to say.

So your feet follow your mind

and your body walks away, [dan walks towards paper, leaving his wallet on table]

you're off on a tangent

your friend has something left to say.

It's not because you don't love him

and we know you care about what he said,

you just have a fantastic idea

you need to get outside your head.

[Dan's solo — Dancing with a piece of paper and creating a paper plane]

Mate!?? [Nathan hands Dan his wallet back]

Now i'm going to take ADHD and split it in half; [Rip paper with ADHD in half]

now we have AD & HD.

Does not this feel like art?? [to Dan].

Attention Deficit, that'll be the first part.

Now I feel like this part of my name

is slightly misleading

because there is no deficit

of attention in the examples I'm seeing.

I just don't hold the attention down,

it's all over the ceiling. it is just

simultaneously firing

on several cylinders.

At this point I should mention that I'm heterogeneous

(definition) I display a different mixture of traits in every single case.

Now let us take 50% creativity, 7% stress, 40% emotion,

3% rest and shove it in a potion.

But sometimes the mixture will have me exploding… [enter Anton]

[Anton… Sword Play.]

Now let's speak about the outbursts and negative connotations,

general misconceptions bring all types of complications.

From outside looking in this behaviour can be unsettling,

emotional outburst can be seen as quite threatening.

And this is the loudest part of me. Snap judgements,

200 mph of over-evaluation can lead to isolation.

I'm as smart as any counter part I've ever faced,

this exam paper's in front of me but my minds all over the place.

My intelligence cannot be defined by standard evaluation,

a SATS test to me is evaluating a fish by its ability to climb a tree.

My imagination extends to the sky and warps with the time,

you will not find it can be simply defined.

But don't think I don't care.

I fear that you think I don't care,

when I care more than I could explain.

I'm charged from emotions that I display, simple and plain.

Every morning I wake up with a renewed sense of hope and enthusiasm,

an almost genuine belief that the issue I face on a daily basis will escape from me,

that is until the remote's in the fridge

and I've misplaced my keys with the excitement for the day on which I leave.

Now picture the child you imagine me to be.

I live with ADHD but whats it like to live with me???

A good thing to address so

we asked a mother and she eloquently said:

"Everything seems like a battle,

walking to school, getting dressed,

an ungodly hour when you're woken from your sleep,

by the loveliest little terror, tugging on your linen sheets.

The days you go for a wee

when you find the floor coated in washing powder".

And she knows, that he knows better and thinks this is enough,

so she despairs and asks why, he answers "just because".

The stress is condensed for hours straight, so she sits

on her hands and gathers the strength to not retaliate.

Then there are the times that she lashes out with

screams and shouts, the apex of stressing out.

Followed by nights of sobbing at the foot of the bed

‘cause she sees her child's angelic face and regrets what was said.

Feels like she failed the person that’s closest to her,

like she didn't give the emotional support, feeling a mess.

Now it seems like all the arguments were over

insignificant events in the absence of heated emotions,

because we sometimes forget that life is just

a collection of moments. Plus he’s only 4 for God’s sake.

Then she spoke of the times of parental pride,

her heart bursts at the seams with love, she feels ec-static.

Every time her boy’s creativity shines through

he does something bloody fantastic.

And the moment when a stranger plays their part

simply by showing a look of compassion rather than contempt.

Sees her child having a meltdown and praises her for how well it was handled

then says something positive about her boy in the same event.

And the nights she goes to bed knowing that she smashed the day,

the boy was completely and utterly perfect in every single way.

His heightened emotions radiating love and expressing it openly,

knowing without her son she’d be completely and hopelessly, lost.

……..

I guess now it feels right to address a

professional and educational setting.

I’m seen as disrupted because

I struggle with focus in a lesson.

But it’s more that I spread my focus in a lesson.

My mind’s awesome, I solve problems,

maybe not the one on the board in front of me,

but i did design a ecosystem based on the workings of a tree.

And there’s a way to get rid of the energy

that is living within;

medication -

so they riddle me with Ritalin.

My mind numb, no longer in an excited state,

the pro of this is, now I can concentrate.

One tablet lasts somewhere between 6 to 8

hours, so that keeps me calm for a working day.

My predicament is kinda’ scary,

feel less and work more

and a fix is only temporary.

…

I don’t profess to have an answer,

I doubt anybody ever will,

I just wanted to explain

both the pride and the pain that I have obtained,

due to a mind that works differently,

and I guess I wanted to tell you that I care.

So if I'm in a chair, and my behaviour makes you want to stare,

I'm inviting you to sit with me,

Appendix 13. Primary Outcome Statistics.

ITT analyses of the primary outcome – carer-rated. Influence of predictors.

Table 39. ITT, carer-rated regression analysis. CGI total change between baseline and 6 months. The influence of covariates

Overall effect of the model: F (5,82) = 4.54, p =.001			**Number of observations = 88**	
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-4.721	3.267	-1.445	.152
hom	1.698	1.573	1.079	.284
NT	2.661	1.553	1.713	.090
Age	.242	.273	.889	.377
ADHD severity	6.040	1.430	4.225	.000
Male vs female	-1.969	1.743	-1.129	.262
Dependent Variable: CGI change score (carer)				

Table 40. ITT, carer-rated regression analysis. Emotional lability change between baseline and 6 months. The influence of covariates

Overall effect of the model: F (5,82) = 4.89, p= .001			**Number of observations = 88**	
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-1.385	1.226	-1.130	.262
hom	1.227	.588	2.089	.040
NT	.648	.583	1.112	.269
Age	.011	.103	.104	.918
ADHD severity	2.177	.535	4.067	.000
Male vs female	-.548	.651	-.841	.403
Dependent Variable: emotion change score (carer)				

Table 41. ITT, carer-rated regression analysis. Restlessness/Impulsivity change between baseline and 6 months. The influence of covariates.

Overall effect of the model: F (5, 82) = 3.53, p=.006			**Number of observations = 88**	
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-3.119	2.479	-1.258	.212
hom	.437	1.188	.368	.714
NT	2.125	1.179	1.802	.075
Age	.208	.208	1.001	.320
ADHD severity	3.939	1.082	3.639	.000
Male vs female	-1.483	1.317	-1.126	.264
a. Dependent Variable: restless/impulsive change score (carer)				

Per protocol analyses of the primary outcome – carer-rated. Influence of predictors.

Table 42. Per protocol, carer-rated regression analysis. CGI total change between baseline and 6 months. The influence of covariates

Overall effect of the model: F (5,69) = 3.61, p= .006			**Number of observations = 75**	
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-3.721	3.456	-1.077	.285
hom	1.653	1.722	.960	.340
NT	3.045	1.605	1.898	.062
Age	.184	.288	.640	.525
ADHD severity	5.417	1.521	3.562	.001
Male vs female	-1.709	1.850	-.923	.359
Dependent Variable: CGI change scores (carer)				

Table 43. Per protocol, carer-rated regression analysis. Emotional lability change between baseline and 6 months. The influence of covariates

Overall effect of the model: F (5,68) = 3.69, p= .005			**Number of observations = 74**	
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-1.157	1.298	-.892	.376
hom	1.015	.642	1.580	.119
NT	.612	.603	1.014	.314
Age	-.009	.108	-.085	.932
ADHD severity	2.088	.568	3.674	.000
Male vs female	-.195	.691	-.282	.779
Dependent Variable: emotion change score (carer)				

Table 44. Regression analysis. Excitability/restlessness change between baseline and 6 months. Per protocol analysis, carer-rated. The influence of covariates

Overall effect of the model: F (5,68) = 3, p=.017			**Number of observations = 74**	
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-2.261	2.631	-.859	.393
hom	.594	1.302	.456	.650
NT	2.585	1.223	2.114	.038
Age	.162	.220	.736	.464
ADHD severity	3.403	1.152	2.955	.004
Male vs female	-1.583	1.400	-1.131	.262
Dependent Variable: restlessness/impulsivity change score (carer)				

ITT analyses of the primary outcome – teacher-rated. Influence of predictors.

Table 45. ITT, teacher-rated, regression analysis. CGI total change between baseline and 6 months. The effect of Predictors

Overall effect of the model: F (5,25) = 2,047, p=.106		**Number of observations = 31**		
	Unstandardized Coefficients			
Predictors	B	Std. Error	t	Sig.
(Constant)	-13.908	6.476	-2.147	.042
hom	.579	2.887	.201	.843
NT	4.113	3.140	1.310	.202
Age	1.194	.569	2.100	.046
ADHD severity	1.338	2.895	.462	.648
Male vs female	6.580	3.843	1.712	.099
Dependent Variable: CGI change score (teacher)				

Table 46. ITT, teacher-rated, regression analysis. CGI emotional lability change between baseline and 6 months. The influence of Predictors

Overall effect of the model: F (5,25) = 1.68, p= .177		**Number of observations = 31**		
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-3.559	1.683	-2.114	.045
hom	.403	.750	.537	.596
NT	.615	.816	.754	.458
Age	.271	.148	1.830	.079
ADHD severity	.308	.752	.409	.686
Male vs female	1.789	.999	1.792	.085
Dependent Variable: emotional lability change (Teacher)				

Table 47. ITT, teacher-rated regression analysis. CGI restlessness/impulsivity change between baseline and 6 months. The influence of Predictors

Overall effect of the model: F (5,25) = 1.8, p= .15		**Number of observations = 31**		
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-10.349	5.362	-1.930	.065
hom	.176	2.390	.074	.942
NT	3.498	2.599	1.346	.190
Age	.924	.471	1.962	.061
ADHD severity	1.030	2.397	.430	.671
Male vs female	4.790	3.182	1.506	.145
Dependent Variable: restlessness/impulsivity change(Teacher)				

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Per protocol analyses of the primary outcome – teacher-rated. Influence of predictors

Table 48. Per protocol, teacher-rated regression analysis. CGI total change between baseline and 6 months. The effect of Predictors.

Overall effect of the model: F (5,17) = .727, p=.613			**Number of observations = 23**	
	Unstandardized Coefficients			
Predictors	B	Std. Error	t	Sig.
(Constant)	-7.161	8.113	-.883	.390
hom	.572	3.161	.181	.858
NT	-1.980	4.154	-.477	.640
Age	.773	.667	1.159	.263
ADHD severity	-1.025	3.301	-.310	.760
Male vs female	3.472	4.458	.779	.447
Dependent Variable: CGI change (Teacher)				

Table 49. Per protocol, teacher-rated regression analysis. CGI emotional lability change between baseline and 6 months. The effect of Predictors.

Overall effect of the model: F (5,17) = .897, p= .505		**Number of observations = 23**	
	Unstandardized Coefficients		
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-1.669	1.891	-.883	.390
hom	.117	.737	.158	.876
NT	-1.156	.968	-1.194	.249
Age	.162	.156	1.043	.312
ADHD severity	-.352	.769	-.458	.653
Male vs female	.296	1.039	.285	.779
Dependent Variable: emotional lability change (Teacher)				

Table 50. Per protocol, teacher-rated regression analysis. CGI restlessness/impulsivity change between baseline and 6 months. The effect of predictors.

Overall effect of the model: F (5,17) = .571, p= .722		**Number of observations = 23**	
	Unstandardized Coefficients		
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-5.493	7.035	-.781	.446
hom	.456	2.741	.166	.870
NT	-.824	3.602	-.229	.822
Age	.611	.579	1.056	.306
ADHD severity	-.672	2.862	-.235	.817
Male vs female	3.176	3.866	.821	.423
Dependent Variable: restlessness/impulsivity change(Teacher)				

Medication status.

Table 51. Regression analysis. CGI change between baseline and 6 months in those taking medication. The effect of predictors.

Overall effect of the model: F (5,54) = 4.28, p = .002		**Number of observations = 60**		
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-2.736	1.572	-1.740	.088
hom	-1.062	1.860	-.571	.570
NT	3.112	1.737	1.791	.079
Age	2.010	1.638	1.227	.225
ADHD severity	6.400	1.642	3.898	.000
Male vs female	-2.029	1.959	-1.036	.305
Dependent variable: CGI change score				
Selecting only cases where participants take medication				

Table 52. Regression analysis. CGI change between baseline and 6 months in those not taking medication. The effect of predictors.

Overall effect of the model: F (5,23) = 2.095, p = .103		**Number of observations = 29**		
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	.827	3.666	.226	.824
hom	4.500	2.767	1.627	.117
NT	.422	2.997	.141	.889
Age	-3.101	2.446	-1.268	.217
ADHD severity	4.188	3.073	1.363	.186
Male vs female	-4.252	3.814	-1.115	.276
Dependent variable: CGI change score				
Selecting only cases where participants do not take medication				

Those with co-occurring autism

Table 53.Regression analysis. CGI change in those with co-occurring autism. Effect of Predictors.

Overall effect of the model: F (5,20) = 2.242, p = .09		**Number of observations = 26**		
	Unstandardized Coefficients			
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-11.658	6.365	-1.831	.082
hom	4.222	3.178	1.328	.199
NT	8.531	2.965	2.878	.009
Age	.681	.476	1.429	.168
Male vs female	-.416	2.913	-.143	.888
ADHD severity	5.143	2.308	2.229	.037
Dependent variable: CGI change score				
Selecting only cases where participants do have autism				

Table 54. Effect size calculations.

Outcome	Completer	Hom					NT				TAU		
			Mean	**SD**	**n**	**Effect size**	Mean	**SD**	**n**	**Effect size**	**Mean**	**SD**	**n**
CGI	Carer	ITT	4.03	5.766	29	.425	4.17	7.56	29	.388	1.55	5.893	31
		Per Protocol	3.7	6.258	20	.356	4.96	6.577	24	**.55****			
	Teacher	ITT	1.27	5.729	11	.069	4.13	10.232	8	.39	.83	6.978	12
		Per Protocol	1.57	6.451	7	.109	-2.5	5	4	**-.504****			
Restless-Impulsive	Carer	ITT	2.38	4.547	29	.198	3.5	5.225	28	.418	1.48	4.523	31
		Per Protocol	2.3	5.11	20	.172	4.22	4.223	23	**.623****			
	Teacher	ITT	1.09	4.505	11	.016	3.88	7.643	8	.421	1	6.281	12
		Per Protocol	1.57	4.995	7	.097	-1	4.243	4	-.339			
Emotional lability	Carer	ITT	1.66	1.95	29	**.793****	.75	3.014	28	.269	.06	2.08	31
		Per Protocol	1.4	1.789	20	**.679****	.87	2.959	23	.325			
	Teacher	ITT	.18	1.471	11	.25	.25	3.012	8	.195	-.17	1.337	12
		Per Protocol	0.0	1.633	7	.117	-1.5	1.732	4	**-.93****			

*** medium effect size of < .5 (in either direction).*

Appendix 14 Health Related quality of life statistics.

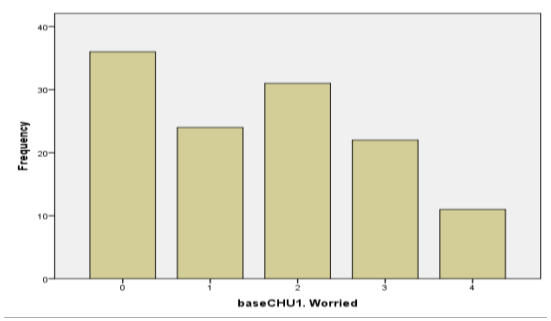
Table 55. Regression analysis. Effect of Predictors. Health related Quality of Life

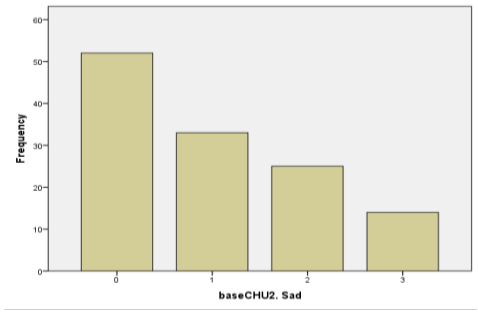
Overall effect of the model: F (5,82) = 1.873, p = .108		**Number of observations = 88**	
	Unstandardized Coefficients		
Predictors	*B*	*Std. Error*	*t*	*Sig.*
(Constant)	-.014	.073	.192	.848
hom	-.057	.031	1.841	.069
NT	-.084	.031	2.730	.008
Age	-.002	.005	.360	.720
ADHD severity	.008	.028	-.268	.789
Male vs female	.047	.034	-1.377	.172
Dependent Variable: wellbeing change (weighted)				

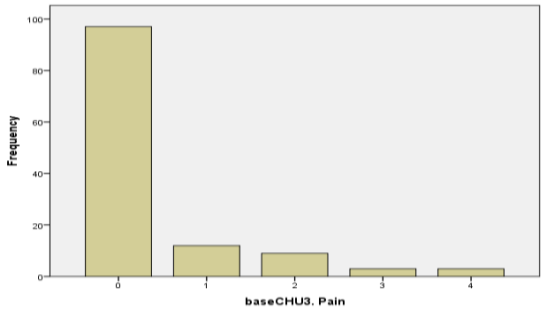
Table 56. Regression analysis. The effect of the interventions on sleep

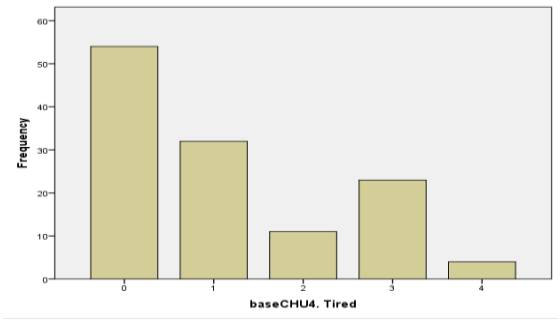
Overall effect of the model: F (5,82) = .481, p= .789		**Number of observations = 88**	
	Unstandardized Coefficients		
Model	B	Std. Error	t	Sig.
(Constant)	.307	.637	.482	.631
hom	.340	.270	1.258	.212
NT	.265	.268	.989	.325
Age	.001	.047	.021	.984
ADHD severity	-.103	.246	-.417	.678
Male vs female	-.223	.299	-.743	.459
Dependent variable: sleep change				

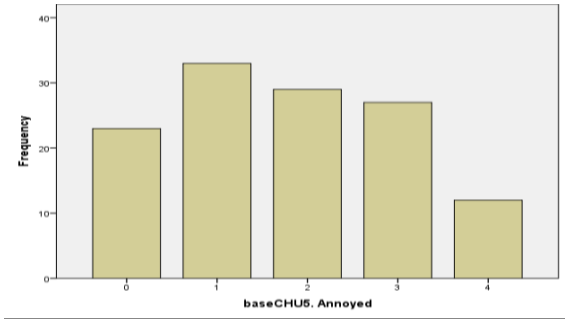
Figure 20. Baseline carer-rated HRQOL status of participants according to CHU-9D individual items

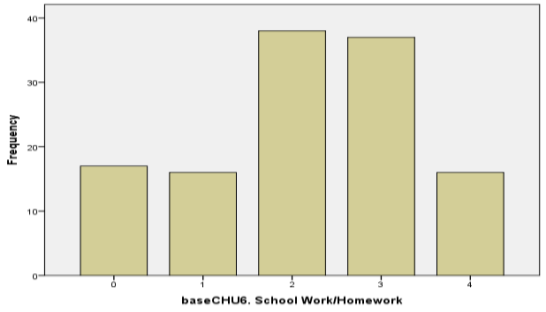


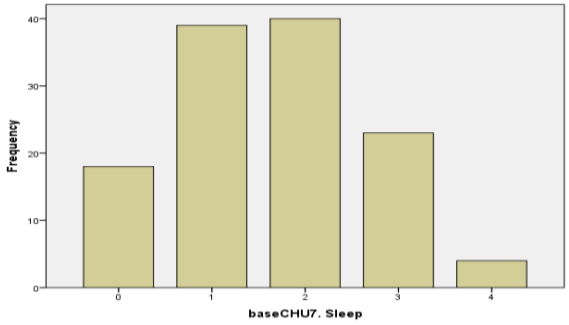


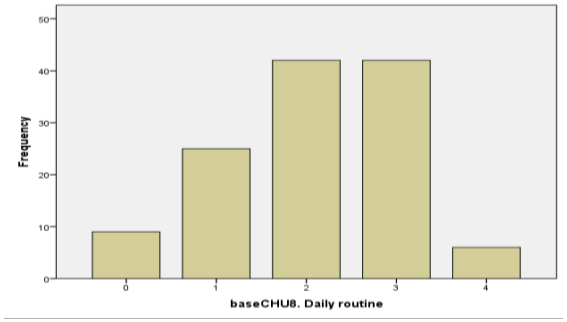


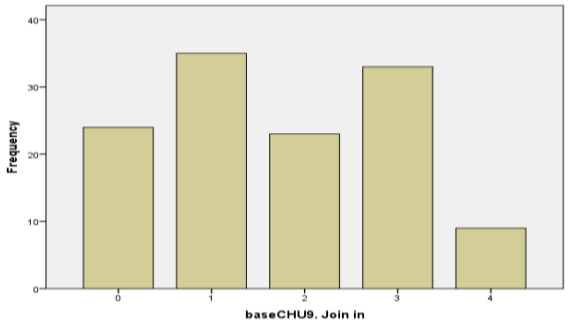






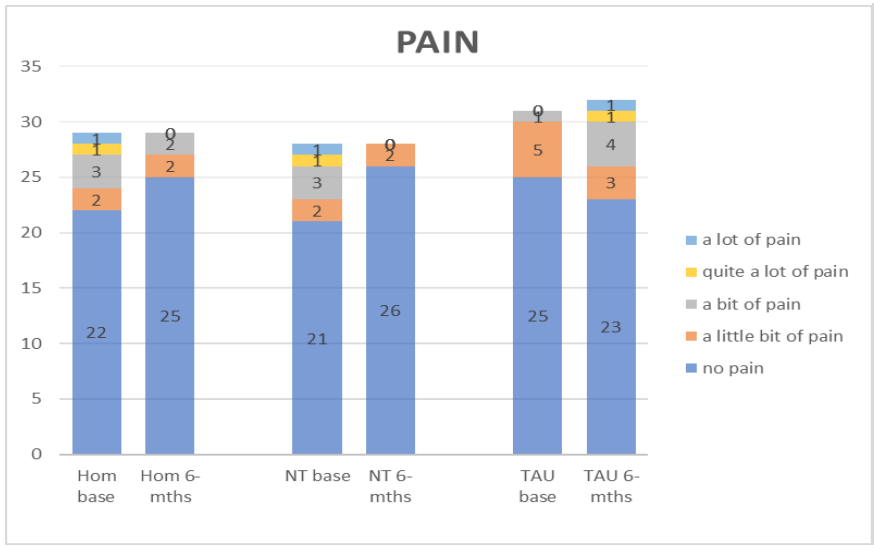


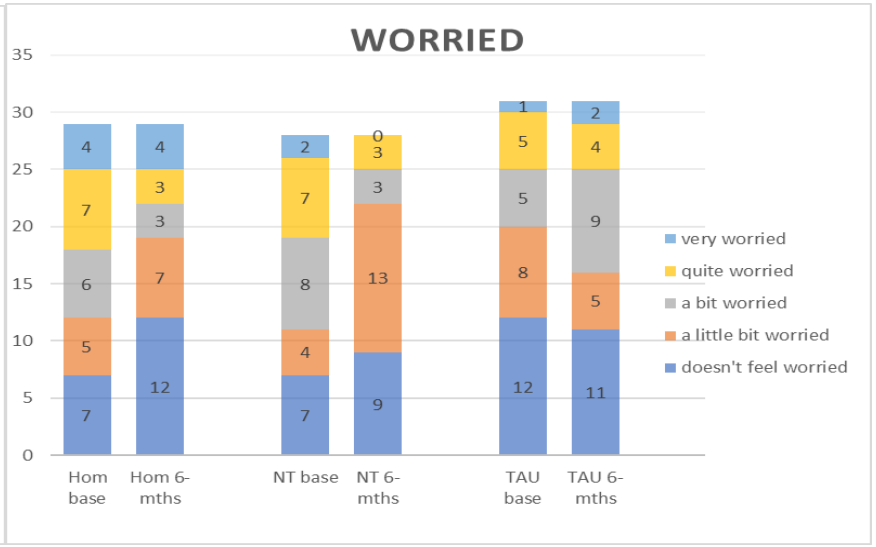


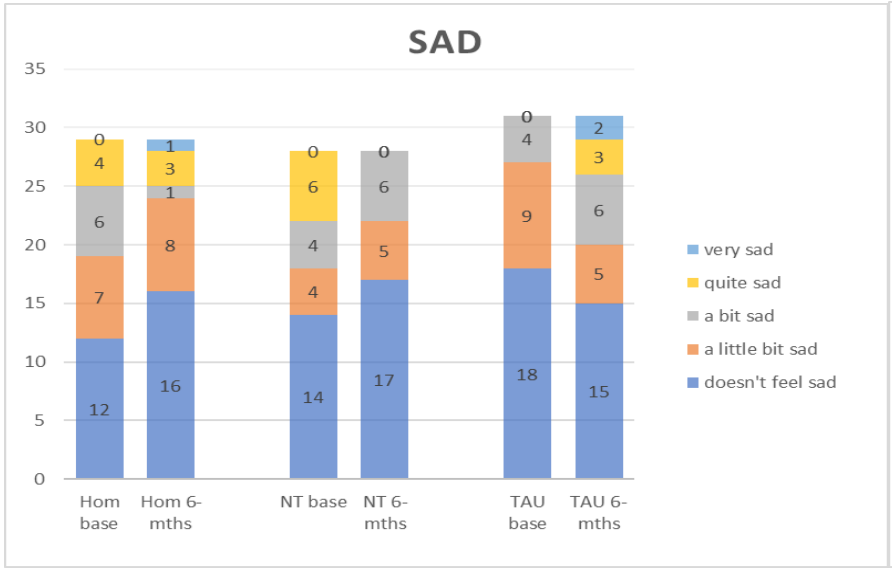


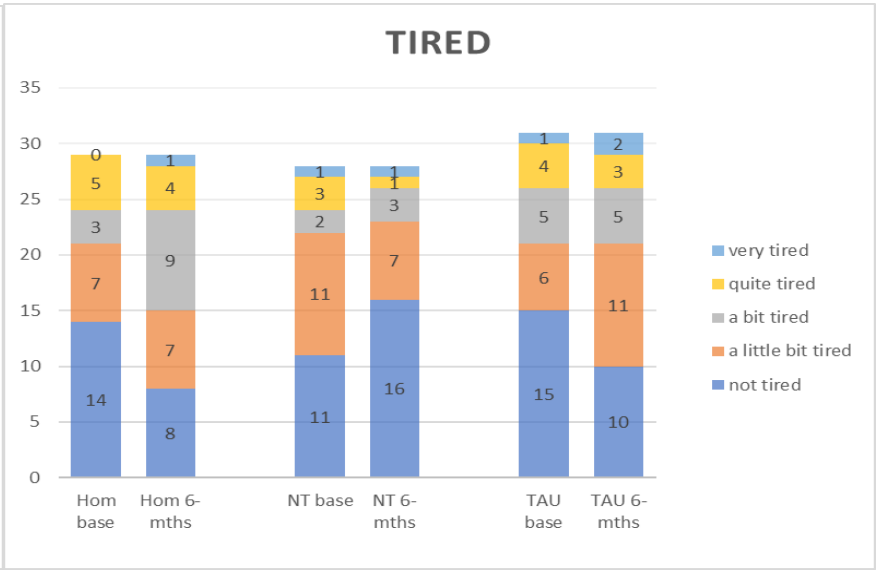
Number of observations = 124

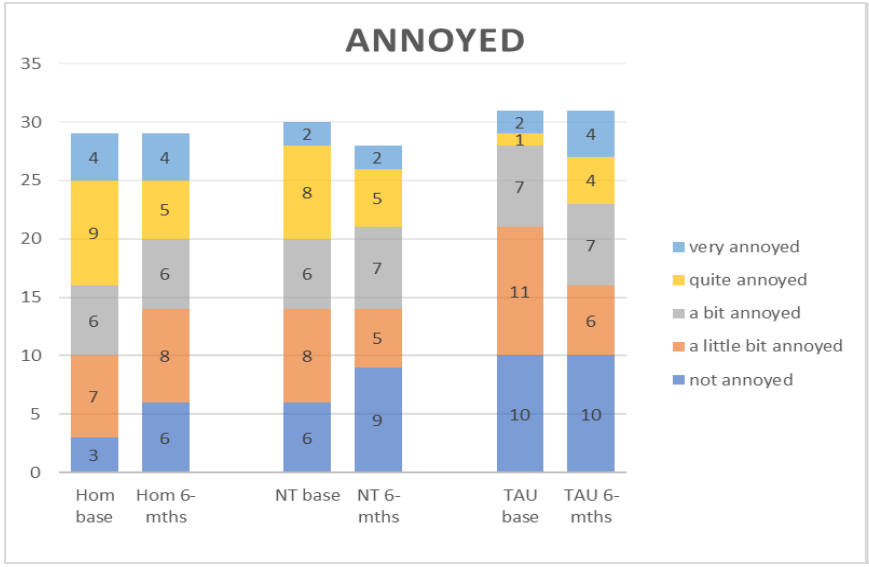
Figure 21. Descriptive graphs of individual CHU 9D items at baseline and 6-months according to group

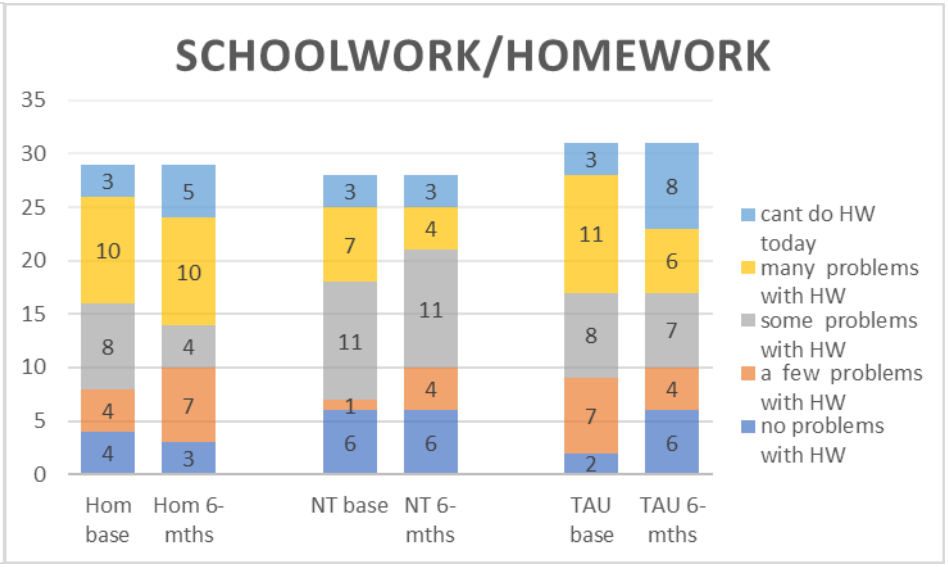


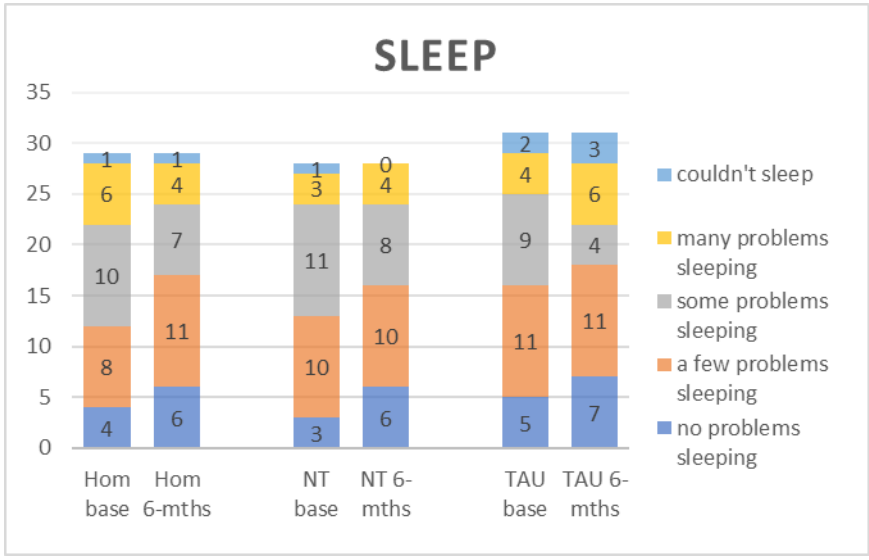


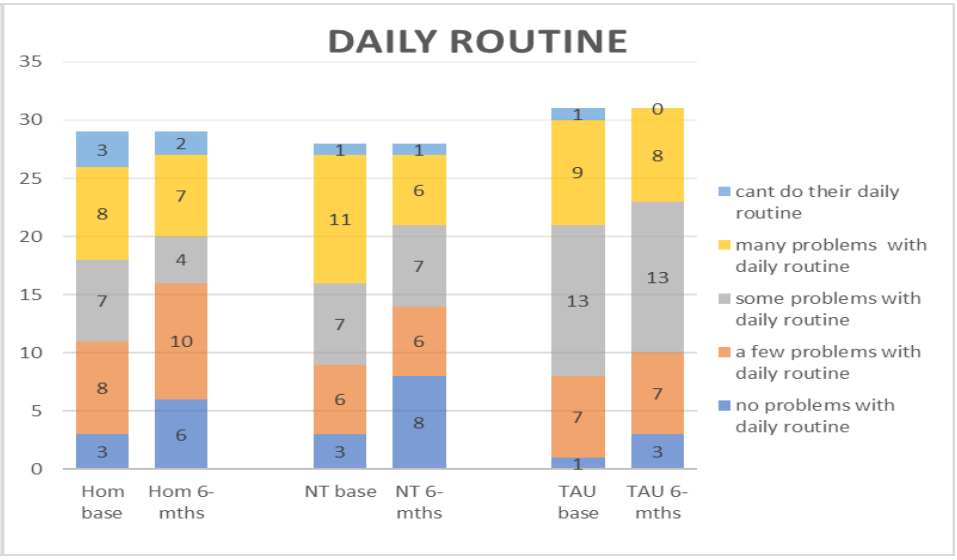


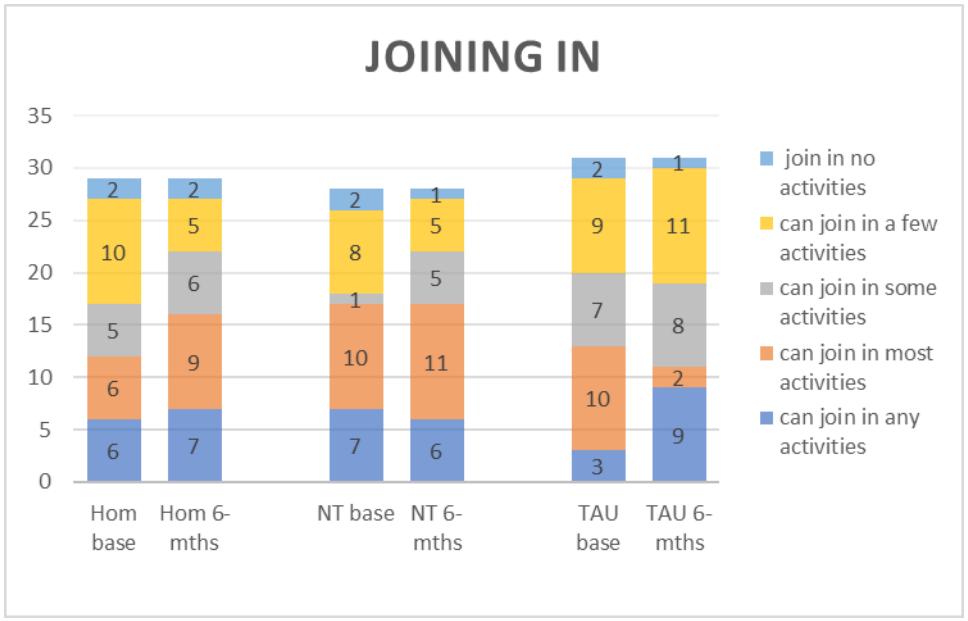



ANNOYED
35
30
25
20
15
10
5
0
Hom base
Hom 6-mths
NT base
NT 6-mths
TAU base
TAU 6-mths
very annoyed
quite annoyed
a bit annoyed
a little bit annoyed
not annoyed


SCHOOLWORK/HOMEWORK
35
30
25
20
15
10
5
0
Hom base
Hom 6-mths
NT base
NT 6-mths
TAU base
TAU 6-mths
cant do HW today
many problems with HW
some problems with HW
a few problems with HW
no problems with HW


SLEEP
35
30
25
20
15
10
5
0
Hom base
Hom 6-mths
NT base
NT 6-mths
TAU base
TAU 6-mths
couldn't sleep
many problems sleeping
some problems sleeping
a few problems sleeping
no problems sleeping


DAILY ROUTINE
35
30
25
20
15
10
5
0
Hom base
Hom 6-mths
NT base
NT 6-mths
TAU base
TAU 6-mths
cant do their daily routine
many problems with daily routine
some problems with daily routine
a few problems with daily routine
no problems with daily routine


JOINING IN
35
30
25
20
15
10
5
0
Hom base
Hom 6-mths
NT base
NT 6-mths
TAU base
TAU 6-mths
join in no activities
can join in a few activities
can join in some activities
can join in most activities
can join in any activities

Appendix 15. Publications and conference presentations related to the thesis

Publications

Fibert, P., Relton, C., Peasgood, T., Daley, D. Protocol for the STAR (Sheffield Treatments for ADHD) project: a pilot study assessing the feasibility of the Trials within Cohorts (TwiCs) design to test the effectiveness of interventions for children with ADHD. Pilot and Feasibility Studies. (2018) 4:61. doi.org/10.1186/s40814-018-0250-3

Fibert, P., Relton, C., Heirs, M., Bowden, D. (2016). A comparative consecutive case series of 20 children with a diagnosis of ADHD receiving homeopathic treatment, compared with 10 children receiving usual care. Homeopathy

Fibert, P. (2015). Case report of a 16 year old youth with diagnoses of attention deficit hyperactivity disorder (ADHD), Asperger's syndrome and dyslexia receiving homoeopathic and tautopathic treatment. European Journal of Integrative Medicine; 7; 3; 312-317

Fibert, P. (2016). Case report of two siblings with multi- morbidities receiving homeopathic treatment for one year. European Journal of Integrative Medicine Volume: 8 Issue: 2 Special Issue: SI Pages: 141-145

Conference presentations

Fibert, P., Relton, C., Daley, D. (2018). Rethinking ADHD intervention trials: feasibility testing of two treatments and a methodology. Oral Presentation. International ADHD Conference. Tel Aviv, Israel.

Fibert, P. (2017). Preliminary feasibility and clinical results of a pilot study of treatment by homeopaths for children with ADHD using the trials within cohorts (TWiCs) design. Oral presentation. Homeopathic Research Institute (HRI), Malta, June 6-8th 2017.

Fibert, P. (2016). The STAR (Sheffield Treatments for ADHD Research) Project, Stage 1: The Feasibility of the Cohort Multiple Randomised Controlled Trial (cmRCT) Design for Testing the Acceptability, Clinical and Cost Effectiveness of Treatments for ADHD. Oral Presentation. Randomised Controlled Trials in the Social Sciences Conference. 7th-9th September 2016, University of York.

Fibert, P. (2016). Rationale for a pragmatic randomised controlled trial of the effectiveness of treatment by homeopaths for ADHD. Homeopathy:105; 1, 28-29 Oral presentation. Homeopathic Research Institute (HRI), Rome, July 2015.

Fibert, P., Relton, C. (2015). Protocol for the Sheffield Treatments for ADHD Research (STAR) Project. Testing the feasibility of the trial design. Poster Presentation. 5th World Conference on ADHD. May 2015. Glasgow.

Fibert, P., Relton, C. (2014). Facilitating a pragmatic comparative trial of the clinical and cost effectiveness of homeopathic treatment for ADHD. European Journal of Integrative Medicine: 6; 610–6. Conference Poster Presentation. Research Council For Complementary Medicine(RCCM), Camstrand. 2014.

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