Intensive behavioural interventions based on applied behaviour analysis (ABA) for young children with Autism spectrum disorder: A systematic review and cost-effectiveness analysis

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Summary of Research

Design*:* Systematic review and individual participant data (IPD) meta-analysis of effectiveness, decision model of cost-effectiveness, budget impact analysis and value of information (VOI) analysis.

Background**:** Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder characterised and diagnosed by early onset difficulties in social communication and restricted repetitive patterns of behaviour activities and interests (1). The high prevalence and serious long term outcomes, as well as the costs of providing high-quality health, educational and community services for this population (2, 3) and their families makes ASD a considerable health concern. The most widespread and advocated of such therapies are those based on applied behaviour analysis (ABA). Despite a number of previous systematic reviews in this area, it remains unclear whether these interventions are effective, cost-effective in the short, and long-term.

Aims of the research: The aims of the research are to evaluate the clinical and cost-effectiveness of intensive ABA-based interventions for young children with ASD based on current evidence; to establish the financial consequences of introducing the intervention in the UK considering the specific budget impact upon national health services, local authority and social care; and, to estimate the value of undertaking additional research in this area.

Design and methods: The question of whether intensive ABA-based interventions are effective for young children with ASD will be addressed by a systematic review and individual participant data meta-analysis (IPD-MA). The results of IPD-MA will inform a decision model to evaluate the cost-effectiveness of the interventions in the UK setting, as will a series of additional systematic reviews of cost-effectiveness, utilities and epidemiological studies as required by the model. Expert elicitation will also be used to address areas of uncertainty and populate the model.

IPD-MA of all relevant controlled studies will evaluate clinical effectiveness and explore whether clinical effectiveness varies between particular types of children. Where we are unable to obtain IPD from study authors, we will carry out an aggregate data meta-analysis to compare with the IPD-MA results.

A new decision-analytic model will be developed to assess the cost-effectiveness of intensive ABA-based interventions for young children with ASD. This model will be used to evaluate the cost per Quality Adjusted Life Year (QALY) of early intensive ABA-based interventions and quantify the main uncertainties facing decision makers. This analysis will include a VOI analysis to quantify the value of undertaking further research to resolve these uncertainties. A budget impact model will also be developed to estimate the financial consequences of introducing the intensive ABA-based interventions for young children in the UK.

Dissemination**:** Findings of the systematic reviews, cost-effectiveness, VOI analysis and budget impact analysis will be reported in an HTA monograph. We will publish the results of clinical effectiveness and economic evaluation as open access articles in peer-review journals, and as a widely accessible summary report directed at patients and a more general audience. The outputs will be of value to clinicians, parent and cares' of children with autism, guideline authors, policy makers and commissioners of services for children with autism.

Background

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder characterised by impaired reciprocal social communication and a pattern of restricted, often non-adaptive repetitive behaviours, interests and activities (1). As a spectrum disorder, the severity and exact manifestation of ASD can vary considerably over time and between individuals, impacting development in different areas (intellectual, communication, social, emotional, and adaptive) (2).

The impact of ASD on individuals and their families can be extensive and is experienced from an early age. This is often complicated by a delay in language development, with a third of people with ASD not developing sufficient natural speech to meet their daily communication needs (3); and an apparent reduced intellectual functioning, with 45% of individuals with ASD scoring less than 70 on standardised IQ tests (4). Additionally, ASD is often associated with reduced adaptive function, medical and psychiatric comorbidities (e.g. epilepsy, gastrointestinal problems, anxiety, depression) (5) and additional functional problems (e.g. sleep, feeding problems). Children with ASD also identify feeling lonely significantly more frequently (6) and there is evidence to suggest they are at increased risk of victimisation and bullying (7). More widely, the families of individuals with ASD report significantly more stress than both those of typically developed children and of other disabilities (8).

ASD is a lifelong disorder, however to date there have been few well-conducted studies of adult outcomes in ASD (9). The long-term outcomes for most people with ASD are reported as poor, with reduced educational attainment, independent living, employment, overall social competence, plus a lack of intimate relationships and high rates of mental health problems (10-12). ASD has been shown to be associated with low levels of engagement in society (13) and low employment levels (14) in later life.

The relatively high prevalence of ASD (around 1.6% of children in the UK (15)) means that it has a significant economic impact. A recent study estimated total costs to the United Kingdom (UK) of ASD to be £32 billion per year, with an average cost of £1.5 million per person with ASD over a life-time (16). Effective early treatment that alters the longer-term course of ASD would therefore have great potential benefits for individuals, families and society (17, 18).

The most widespread, advocated early intervention therapies are those based on applied behaviour analysis (ABA) first proposed by Lovaas (19). These intensive intervention approaches, recommended for use early in the child's development, target a broad range of skills and adaptive behaviours with the proposed aim of redirecting the child to a developmental trajectory with better outcomes. Early intensive behavioural intervention (EIBI) models use the principles of ABA to provide a comprehensive approach to teaching. These promote techniques (such as the breaking down of skills into their basic components) that emphasise repetition of tasks and positive reinforcement. The approach is designed to target preschool children, often on a one-to-one basis, for 20 to 50 hours per week (20).

Critiques of EIBI have focused on the limitations of the use of highly structured sessions. While such teaching techniques may be effective in teaching specific skills, concerns have been raised about the risk of precipitating the emergence of challenging behaviours, a lack of child spontaneity, and an over reliance on prompts (21). Additionally, it has been suggested that these methods further restrict the child's capacity to develop generalisation skills, something which children with ASD commonly find difficult (21). In response, a number of adaptations of the original model have been developed that incorporate the principles of ABA into a more naturalistic framework. Known collectively as Naturalistic Developmental Behavioural Interventions (NDBIs) (21), these include child-led and incidental training opportunities. Prominent examples of these models are Pivotal Response Training (PRT) (22), the Denver model (23), and its derivative the Early Start Denver Model (ESDM) (13). While still encompassing the fundamentals of ABA methodology such as discrete trial training and taking a comprehensive approach to skills development, the proponents of these models report that the revised intervention programmes address the methodological flaws in the original EIBI model and implement a more multi-faceted intervention able to meet the individual needs of children with ASD and their families.

Early intensive ABA-based interventions are used in a number of countries including Canada, Norway, and the United states (US) (24). In the US, most of the 44 states that explicitly mandate coverage of autism treatment favour ABA-based interventions and 24 of these states have passed legislation to establish professional regulation of ABA providers (25). By contrast, most European countries have favoured a more eclectic approach to early intervention strategies (26).

Current National Institute for Health and Care Excellence (NICE) guidelines (27, 28) on the diagnosis, management and support of children and young people with autism recommend "a specific social communication intervention" for the treatment of the core features of ASD. While some techniques (e.g. therapist modelling, video-interaction feedback) are recommended in the management pathway, a specific intervention model is not. For behaviour that challenges, the NICE guideline recommends offering a psychosocial intervention (informed by a functional behavioural analysis) as a first-line treatment. A recently published survey of 111 UK parents of children with ASD reported that a majority received speech and language therapy (62%), with only 18% receiving any form of behavioural intervention and 25% receiving no intervention at all.(29)

Current evidence for early intensive ABA-based interventions

A number of systematic reviews (2, 17, 18, 30-36) have reported early intensive ABA-based interventions to be beneficial for children with ASD, demonstrating improvements in developmental functioning, decreased maladaptive behaviour and reduced symptom severity (2, 17, 30-32, 34, 35). However, these have suffered from a series of limitations and not been able to provide a definitive assessment of the clinical effectiveness and cost-effectiveness of ABA-based interventions on which to base policy recommendations/guidelines.

Firstly, there is considerable variation in the response of children to early intensive ABA-based interventions (17). A number of the reviews investigated factors that may influence response, suggesting that child characteristics such as age, IQ, adaptive behaviour and verbal ability at intake may moderate the effectiveness of the intervention (2, 17, 32, 34, 36). However, these analyses were based on aggregate data with little power to detect differences and the potential to mislead. The conclusions of these analyses are often inconsistent and potentially subject to problems of ecological fallacy (where inferences about the nature of individuals are deduced from inference for the group to which those individuals belong). The one review that used individual participant data (IPD) (31) requested only four data items (age, IQ and adaptive behaviour scores at intake and after 2 years) and was therefore unable to isolate potential effect modifiers.

Secondly, the inclusion criteria applied across these reviews has been inconsistent, with the majority taking a narrow interpretation of early intervention models and focusing on EIBI alone to the exclusion of other early intensive ABA-based interventions. Consequently, there are no systematic reviews that have evaluated the effectiveness of the broad range of ABA-based therapies available and none which seek to compare the relative effectiveness of different early intensive ABA-based interventions. Evaluation of the quality of primary studies in the majority of the systematic reviews was often inadequate, with little attempt to properly integrate the impact of study quality into the synthesis of evidence (17, 35). This is crucial given the methodological weakness of much of the primary evidence. Since the publication of the most recent review (35) a number of primary studies of early intensive ABA-based interventions have been published including at least one randomised controlled trial (RCT) (37).

Finally, in preparation for this application, we have not identified any existing systematic reviews of cost-effectiveness. However, our initial searches identified four evaluations of the cost-effectiveness of early intensive ABA-based interventions in the US, Canada and the Netherlands.(38-41). All four of these cost-minimisation studies found early intensive ABA-based interventions to be cost-saving. These studies, however, lack relevance to the UK setting and utilise very simplistic static approaches to modelling the relationship between short-term outcomes and medium to long-term outcomes. There is therefore lack of evidence regarding the cost-effectiveness of early intensive ABA-based interventions in the UK.

Evidence explaining why this research is needed now

The long-term health implications and the significant economic burden of providing care means that there is an urgent need to improve outcomes for people with ASD. If effective, early intensive ABA-based interventions have the potential to improve the quality of life of people with ASD while reducing the economic burden of ASD. Current systematic reviews are, however, unable to provide a definitive assessment of the clinical and cost-effectiveness of early intensive ABA-based interventions. Further, these reviews have primarily been based on aggregate data and therefore have had only limited success in identifying children for whom early intensive ABA-based interventions are likely to be most effective. These limitations collectively point to the pressing need to conduct a comprehensive review with wider inclusion criteria that examines subgroup mediators through IPD analysis. Furthermore, given the substantial resources required to implement early intensive ABA-based interventions and the lack of any comprehensive cost-effectiveness analysis it is vital that a proper assessment of the cost-effectiveness be carried out to ensure that the benefits of implementing early intensive ABA-based interventions outweigh the costs.

The lack of clear research evidence to guide clinical practice, regarding the effectiveness of early intensive ABA-based interventions may, however, mean that further primary research is warranted. This will be explored in detail in our research by using value of information (VOI) methods to evaluate the value of undertaking research to reduce decision uncertainty (42-44). Without a proper assessment of the research needs, there is a risk that funding, and clinical and patient effort will be wasted on unnecessary or sub-optimal studies, which may do nothing to reduce the key decision uncertainties. It is therefore timely to both assess decision uncertainty and to evaluate the cost-effectiveness of resolving that uncertainty. The results of such an exercise will provide a foundation for future decisions about the need, and requirements for, further primary studies of ABA-based interventions for young children with ASD.

Aims and objectives

The aims of the proposed research project are to: establish the clinical and cost effectiveness of intensive ABA-based interventions for young children with ASD; to identify key subgroups or effect modifiers that impact on the clinical and cost-effectiveness of early ABA-based intensive interventions; and, to establish the value of carrying out further research into the clinical effectiveness of intensive ABA-based interventions for young people with ASD.

The key objectives are:

- To identify in a comprehensive manner all relevant studies;
- To determine the clinical effectiveness of intensive ABA-based interventions for young children with ASD compared to usual care by conducting aggregate data and IPD meta-analyses of data from all available comparative studies;
- To undertake utility, cost-effectiveness epidemiology reviews to inform the design and identify key clinical parameters for a decision model;
- To model the cost-effectiveness of early intensive ABA-based interventions for ASD by developing a *de novo* decision model, including an assessment of cost-effectiveness in any sub-group identified in the clinical effectiveness review;
- To develop a budget impact model based on the cost-effectiveness analysis;
- To undertake a VOI analysis to inform future research priorities.

Systematic reviews and meta-analysis

We will conduct a comprehensive systematic review and IPD meta-analysis to identify clinical effectiveness evidence of intensive ABA-based interventions for young children with ASD. The IPD approach will enable more flexible and robust analyses than are possible with traditional systematic reviews of aggregate data and will facilitate exploration of individual characteristics that may be associated with greater (or lesser) benefit from intervention (45-48).

In addition, the economic model development and parameterisation will be supported by a systematic review cost-effectiveness studies and pragmatic reviews of utilities and epidemiological studies.

The systematic reviews of clinical and cost effectiveness will be conducted according to the general principles recommended in the Centre for Reviews and Dissemination (CRD) guidance on the conduct of a systematic review (49) and reported according to the general principles of the PRISMA statement (50) The research protocol will be written in accordance with the PRISMA-P initiative, and registered on the international prospective register of systematic reviews (PROSPERO).

Protocol development

A full protocol based on the methods outlined below will be developed with input from expert advisors and study investigators who agree to provide individual-level data for analysis.

Study identification

We will search the following bibliographic databases to identify potentially relevant studies: Cochrane Central Register of Controlled Trials (CENTRAL); CINAHL, Embase, ERIC, MEDLINE, PsycINFO and Social Science Citation Index. The draft strategy for MEDLINE (OvidSP) given in Appendix 1 will be refined and also amended as appropriate for use with the other databases. No date or language limits will be applied. Records identified from the database searches will be downloaded and imported into EndNote bibliographic software and de-duplicated. Reference lists of relevant systematic reviews will also be searched manually.

As publication bias has been identified as a concern in relation to early intensive ABA-based interventions in ASD (51), we will also attempt to identify grey literature by searching for conference papers (using Embase and Conference Proceedings Citation Index) and dissertations and theses (using PsycINFO and Proquest's Dissertations & Theses: UK and Ireland). Clinical advisors and authors of identified studies will be asked to identify any additional potentially relevant studies, particularly those that are unpublished. We will also search ClinicalTrials.gov and the WHO ICTRP to identify any studies in progress.

Update searches will be conducted towards the end of the project to ensure that we identify any recently published studies.

Study selection criteria

Participants

Studies that include children with a diagnosis of Autistic Disorder, Asperger's Disorder, Pervasive Development Disorder - Not Otherwise Specified, Atypical ASD (52) or Autism spectrum Disorder (1) will be included. Since evaluations of early intensive behavioural interventions have not consistently investigated the same range of ages in children with ASD, inclusion will not be restricted by age. However, where possible, age will be considered in the analysis for relevant subgroups (e.g. pre-school aged children).

Interventions

Intensive behavioural interventions based on ABA will be eligible for inclusion in the review. This includes EIBI, PRT and ESDM models.

Intensive behavioural interventions will be defined as:

- >15 hours per week
- Using a comprehensive approach, targeting a range of behaviours, as opposed to a narrowly targeted intervention aimed at one single behaviour (e.g. joint attention)
- Following a functional analytic approach to treating problem behaviours
- ABA-based teaching strategies (e.g. Discrete Trial Training) and data-driven decision protocols delivered face-to-face by qualified and trained staff to children with ASD
- Delivered at least initially on a one-to-one basis
- Qualified supervision of the therapist delivering the intervention

In line with the commissioning brief, interventions where the therapist is primarily focused on parents will be excluded; however, studies that involve a degree of parental involvement will be included if the other criteria are satisfied. The influence of parental involvement will be explored if such data are available. Detailed final selection criteria will be agreed by the expert advisory group during preparation of the review protocol.

Comparators

Relevant comparators will include all other forms of early intervention such as augmented forms of communication (The Picture Exchange Communication System; PECS), other speech and language therapy interventions, support programmes led by independent providers such as charitable and third sector organisations, educational based structured teaching approaches such as Treatment and Education for Autistic and related Communication and Education for Handicapped Children (TEACCH)(53) and 'eclectic' approaches, as well as placebo, waiting list or 'treatment as usual' groups. Detailed information on comparison groups will be obtained wherever possible to establish the degree to which the interventions resemble current UK practice.

Outcomes

Inclusion will not be restricted by outcome. While evaluations often measure the narrow focus of the intervention- such as 'joint attention' skills or learning how to play specific games, we anticipate studies will also report cognitive, adaptive or social abilities, communication/language skills, ASD symptom severity, or quality of life measures using standardised assessments, parent or teacher rating scales, or behavioural observation. As a core set of outcome measures has not been established in this area (54), inclusion will not be restricted by specific scale or measurement tool. Outcomes analysed in the IPD meta-analysis will, however, be limited to those identified as most important by the advisory group and essential for the economic modelling. This is to ensure the project remains feasible.

Study designs

Randomised and non-randomised controlled trials meeting all other inclusion criteria will be eligible for inclusion.

Study selection

Two reviewers will independently screen all titles and abstracts retrieved from electronic database and other searches. Full paper manuscripts of any publications that may be relevant will be obtained (where possible) and the relevance of each study assessed by two. Relevant non-English language studies will be translated wherever possible. Studies that do not meet all of the criteria will be excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies will be resolved by consensus and, if necessary, a third reviewer will be consulted.

Risk of bias and quality assessment

Critical appraisal of included studies will be based on assessment of trial publications, protocols, and by checking received datasets. Risk of bias in RCTs will be assed using the Cochrane Risk of Bias tool (55). Non-randomised controlled study designs will be assessed using the ROBINS-I tool (56).

As well as assessing aspects of bias (such as blinding and/or independence of outcome assessors), where possible the critical appraisal will also assess the fidelity of delivered interventions to the underlying treatment model. Assessment will be undertaken independently by two researchers with any discrepancies resolved by consensus or recourse to a third researcher if necessary.

Data collection and extraction

IPD

Authors of all eligible studies will be contacted and invited to collaborate in the project by contributing individual participant data for inclusion in the IPD meta-analysis and forming a collaborative group who will contribute to protocol development, interpretation of results, and in whose name the IPD meta-analysis will be conducted. On setting up the collaboration a data sharing and data transfer agreement will be put in place with the contributing authors outlining that data will

be anonymous, held securely, used expressly for the purpose of the review and with access restricted to the IPD-MA team.

A common coding system will be developed and data from all studies will be converted accordingly. This will be provided to all collaborators as a preferred option for supply of data, but IPD will be accepted in any coding system (with appropriate meta-data/descriptors provided) and in any suitable electronic format.

Simple checks on the data will be made to ensure data are correctly coded, that missing data are correctly identified and where appropriate that variables are internally consistent. Each data set will also be compared with published results, bearing in mind that there may be differences between these, e.g. if any participants were excluded from the original analyses.

The final data requirements will be listed in the protocol, following consultation with the project advisory and collaborative groups. Anonymised data will then be requested from all members of the IPD meta-analysis collaborators. This will include:

- Baseline data: Study identifier, unique ID, date of recruitment, age, sex, type or measure(s) of ASD, cognitive function, IQ, symptom severity measures
- Treatment received: type of ABA-based early intervention, total duration, intensity (hours per week), total hours, role of parents
- Outcomes: Adaptive behaviour scores, ASD symptom severity, IQ, cognitive skills, behavioural skills, communication (e.g. Vineland Adaptive Behaviour Communication domain), language skills (e.g. Reynell Developmental Language Scales) and any other relevant outcomes at post-intervention and subsequent follow-up periods.

Data storage and confidentiality

All IPD will be received via secure FTP transfer or encrypted email. All data will be anonymised and held in a password-protected area of the CRD server. Access will be limited to staff working directly on the project. Copying data to laptop computers or memory sticks will be prohibited.

Aggregate data

The IPD will be the primary source of data used in the analyses of effectiveness. While every effort will be made to obtain IPD data from all identified studies, if authors have not agreed to share data by month 10 of the project we will proceed with the analysis of the available IPD. For any eligible study where IPD are not available, aggregate data will be extracted from published material. Data from any such studies that have multiple publications will be extracted and reported as a single study. Data extracted will correspond to those listed above. Data extraction will be undertaken by one researcher and checked by another, with discrepancies resolved by consensus, or consultation with a third reviewer, where necessary.

Data analysis

IPD meta-analysis

IPD will be combined in meta-analyses where studies are sufficiently consistent in their characteristics for this to be feasible. Dichotomous outcomes will be analysed by calculating the relative risk for the effect of intensive behavioural interventions compared to control groups. Odds ratios may be used where the relative risk cannot be computed. For continuous outcomes mean differences between treatment arms will be reported. Both “two-stage” models (where effect estimates are calculated for each study, and subsequently pooled in a meta-analysis) and “one-stage” models (where all IPD from all study are analysed together) will be used.(45, 47, 57)

Two-stage models

Two stage models will be fitted as an initial step for all analyses. Effect estimates (relative risk or mean difference) will be estimated for each study and then combined using random effects meta-analysis. Heterogeneity will be assessed using the I^2 statistic (58). This will generate forest plots

enabling results across trials to be compared visually, heterogeneity investigated and differences across subgroups visualised. These will be essential in fully understanding the underlying dataset, and motivating the choice of more complex one-stage models.

One-stage models

If feasible, one-stage analyses will pool IPD from all studies using a generalized linear mixed model framework, which accounts for potential heterogeneity across studies. For continuous outcomes linear mixed models will be fitted. For dichotomous outcomes logistic mixed models will be used to calculate relative risks, or odds ratios where relative risks are computationally intractable.

Exploring clinical heterogeneity and subgroup analysis

The impact of trial-level characteristics (such as type of intensive behavioural intervention delivered) and participant-level covariates (such as age and ASD severity at baseline) on the efficacy of ABA-based treatment (that is, intervention covariate interactions) will initially be examined by dividing trials and participants into suitable subgroups for each covariate of interest and performing meta-analyses within each subgroup. Results will be presented in forest plots to visually assess the impact of covariates. If feasible, the more formal analysis of interactions will use one-stage models, where treatment covariate interactions are added to existing one-stage models for treatment effect. This will enable us to take account of multiple participant characteristics when comparing intervention with comparator and will also enable exploration of potential treatment interactions in a multivariable way. We will compare models, in terms of goodness of fit and parsimony using the AIC statistic. Where appropriate, stepwise regression will also be used to select the "best fitting" model.

Missing data

We will make every effort to minimize the amount of missing data, including requesting information for any enrolled participants that were excluded from the original study analyses.

Where outcome and covariate data are missing for some participants in the overall data set, a complete case analysis will be used in the first instance (i.e. excluding patients with missing data). If there are substantial missing data (around 10% for any outcome or covariate) multiple imputation within each trial will be used to impute missing variables. Sensitivity analyses based on best and worst case scenarios will be used to assess the impact of missing outcome data.

Combining aggregate and individual participant data

Where IPD are not available for relevant studies we will seek to combine aggregate data and IPD in meta-analyses using two-stage methods as described above and, time-permitting, using more advanced methods which have been described elsewhere (59). Results from these analyses will be compared to analyses of aggregate data only and of IPD only as a sensitivity analysis.

Economic evaluation

We propose to develop a new decision-analytic model to assess the cost-effectiveness of intensive ABA-based interventions for young children with ASD. Details of our proposed model are described below.

Intervention and comparators

The intervention in the model will be defined in line with the clinical effectiveness review. Depending on the analysis of clinical effectiveness, if appropriate, the model will present separate analysis for each distinct early intensive ABA-based interventions such as EIBI or PRT. With respect to defining usual care in the UK, we are aware that current practice in the UK is heterogeneous and includes a variety of interventions. (26) To keep the number of analyses feasible and to ensure that they are useful to decision makers, we will present results for distinct comparator therapies only where there is clear evidence of them being widely used in UK practice. This will include the use of no intervention.

Model structure

We anticipate the model will use a cohort simulation approach. This structure will allow for increased flexibility over a more typical Markov model and better accommodate the heterogeneous trajectories

of people with ASD. Following the approach taken in previous cost-effectiveness analyses of early intensive ABA-based interventions, the proposed model will separate an individual's lifetime into distinct phases e.g. early childhood (approx. 3 to 12 years of age), adolescent and early adulthood (approx.13 to 21 years of age) and adulthood (22 years age onwards). (38-41) This allows the model to reflect the short, medium and long-term impact of early interventions, and the different needs and resources that people with ASD utilise over their lifetime, as well as reflecting the changing role of carers and family.

A central challenge for the economic modelling will be reflecting how potential improvements in outcomes such as cognitive function and adaptive behaviour gained in early childhood impact on the trajectory of individuals over the short, medium and long terms, since many of the clinical studies have relatively short follow-up periods. We will seek to incorporate any long-term follow up data that is identified in the clinical effectiveness review into the model. However, we anticipate that it will be necessary to extrapolate the short-term outcomes reported in the clinical studies over the long-term. To represent these relationships appropriately, the proposed model will incorporate epidemiological evidence on the long-term prognosis of children with ASD (10, 60, 61), with an emphasis on making explicit assumptions about the relationship between short-term measures such as cognitive function and adaptive behaviour and medium and long-term outcomes which are likely to include measures of functional status such as adaptive behaviour and non-health outcomes such as residential status and education attainment.

Key parameters and populating the model

- ***Clinical effectiveness:***
  Clinical effectiveness data will be drawn from the IPD meta-analysis and will then be linked to medium and long-term outcomes based on the epidemiological evidence.

- ***Demographic and clinical parameters:***
  The key parameters will be the characteristics of the population being considered, long term prognosis of people with ASD and mortality of people with ASD. These will be identified through a review of the epidemiological literature.

- ***Heath related Quality of life:***
  Recognising that ASD impacts on the quality of life of both individuals with ASD as well as their family and carers', the economic model will incorporate the impact of early behavioural interventions on both individuals with ASD and, if feasible, their carers'. A review of utility scores will be carried out to identify appropriate values for both people with ASD and their carers'.

- ***Resource use and unit costs:***
  Resources utilisation for individuals with ASD is complex, it is generally tailored to the individual needs and often changes over their lifetime. The care and support provided in the UK involves different sectors such as health, education and social service. Therefore, the proposed model will aim to capture these key areas of resource use. Resources utilisation data will be sought from published sources, national surveys and consultation with clinical experts and service providers. All resources used will then be costed by applying unit costs, in UK pounds sterling, for the financial year 2016–2017 (or appropriate year). Unit costs will be obtained from published sources, national surveys, mainstream retailers of non-prescription drugs, and government departments for school costs.

Initial searches suggest that there may be very little published evidence to inform the values of some of the input parameters. We will therefore hold a workshop with a group of clinical experts at which opinion will be sought on parameter values that we are not able to specify from published sources, if necessary an interactive elicitation exercise will be designed to generate estimates of the relevant unknown parameters with uncertainty. The clinical experts will also be consulted on the plausibility of assumptions made in the model and its face validity.

Outcomes
In line with current methods used NICE Guidance and NICE Technology Appraisals (62) will present the outcomes of the model in terms of cost per QALY gained and cost per life year. We will, however, also present the results of the model in terms of a wider range of outcomes relating costs to measures of social function and indicators of intervention success such as educational attainment and residential status.

Sub-group analysis
Heterogeneity in cost-effectiveness will be investigated by clinically important subgroups identified in the clinical effectiveness review. For each subgroup, separate incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves will be presented.

Time horizon
The model will take a lifetime horizon to ensure that all costs and benefits of early intensive ABA-based interventions are captured.

Perspective
The analysis will take the perspective of the National Health Services and Personal Social Services. If feasible, a broader public sector perspective provider perspective will be considered to reflect the impact of the interventions on health, social care and education.

Discounting
Costs and benefits will discounted at 3.5% per annum, in line with NICE Guidance.(62) We will also explore alternative discount rates in a sensitivity analysis.

Modelling uncertainty
Uncertainty in the data used to populate the economic model will be characterised. A probabilistic model will be developed, with each input entered as an uncertain parameter with an assigned probability distribution representing its uncertainty. Monte Carlo simulation uses this distribution to take account of and reflect parameter uncertainty in the overall results. This ultimately helps decision makers understand that, in choosing to implement/not implement an intervention, there is a likelihood of making an incorrect decision (decision uncertainty). This will be presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

Scenario analysis will be used to test the robustness of the cost-effectiveness results to changes in the structural assumptions of the model. Sensitivity analyses will also be used to evaluate the impact of key methodological assumptions on the results.

Value of information analysis and identifying key areas of uncertainty
As part of the economic evaluation, we will identify key areas of uncertainty and undertake a VOI analysis to establish the value of undertaking further research to resolve these uncertainties. VOI analysis allows us to quantify the expected benefits of further research by estimating the value of reducing uncertainty in decisions. This can be estimated by considering the costs of making an incorrect decision about the implementation of an intervention and considering the impact of reducing uncertainty on these costs. The VOI analysis will estimate the expected value of perfect information (EVPI) and value of partially perfect information (EVPPI). This can be compared to the costs of conducting further research in order to help inform recommendations for primary research and help assess whether further primary research would represent value for money.

Budget impact
A budget impact model will be developed to estimate the financial consequences of introducing early intensive ABA-based interventions in the UK. As part of this analysis, we will consider the specific budgets impacted upon (e.g. local authority, NHS, education), as well as where any reductions in costs are likely to accrue (e.g. potential reductions in care and education costs). This analysis will highlight any specific budgetary challenges associated with implementing early intensive ABA-based

interventions and allow decision makers with different perspective (local authority vs NHS) to consider the financial implications of implementation.

Dissemination and projected outputs

The research protocol for the systematic review is registered on PROSPERO (ID:CRD42017068303). We will publish findings of each component in the proposed project in high profile mainstream and specialist journals, such as the British Journal of Psychiatry, the Journal of Child Psychology or Journal of Autism and Developmental Disorders. To disseminate the findings of our research to healthcare professionals and academics the results will also be presented at two conferences: one UK (probably the Child and Adolescent Psychiatry National conference) and one international (probably the International meeting for autism research (IMFAR)).

We also seek to disseminate the findings of our research via number of other channels. This will include:

- Preparation and dissemination of a briefing paper aimed at communicating our findings with commissioners and other stakeholders including parents and professionals working with young people with ASD. This paper will be published on relevant websites such as the National Autistic Society, ASD and child mental health websites, as well as the Newcastle University ASD-cohort and CARGO-NE and University of York's websites. Social media such as twitter will also be used to disseminate key findings.
- Aiming to ensure coverage of our findings in the wider media by issuing a press release.
- Notifying relevant policymaking groups of our research findings. We would expect our findings to have an influence on subsequent future updates of the guidelines for autism spectrum disorder in under nineteens.

Plan of investigation and timetable

Proposed project timetable:

	Month																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Systematic review																		
Protocol development	■	■	■	■														
Literature searches		■	■	■														
Screening and study selection		■	■	■	■													
Obtaining IPD				■	■	■	■	■	■	■	■							
Data extraction, quality assessment and checking				■	■	■	■											
Data Processing (IPD)										■	■	■						
Synthesis and data analysis (aggregate and IPD)							■	■	■	■	■	■	■	■				
Economic evaluation																		
Protocol development		■	■	■														
Literature searches (cost, epidemiology and QoL)			■	■	■													
Screening and study selection			■	■	■	■												
Data extraction, quality assessment and checking						■	■											
Model planning (structure, key parameters)		■	■	■	■	■	■	■	■									
Cost model development (obtain parameter estimates, populate model, other related activities)								■	■	■	■	■	■	■				
VOI and budget impact analyses													■	■	■	■		
Dissemination phase															■	■	■	■
Draft report														■	■	■	■	■
Three Advisory Group meetings and team meetings	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Key milestones

Month 4 Finalise clinical systematic review protocol

Month 5: Complete screening and selection of studies

Month 7: Complete model related reviews

Month 9: Finalise cost-effectiveness model plan

Month 11: End of individual patient data collection

Month 14: Complete final analysis of clinical data and finalise cost-effectiveness model

Month 16: First draft of final report

Month 18: Final draft of NIHR report

Project management

Ann Le Couteur and Robert Hodgson will take overall responsibility for delivery of the project with Mark Rodgers responsible for the management of the systematic reviews and Robert Hodgson responsible for the management of the health economics elements, with support from senior members of academic staff. Financial and research management support will be provided by University of York central services.

This team will meet throughout the duration of the project, with the frequency of meetings determined by need: they will be at least once a month, but more frequently initially. The team will also meet at regular intervals with the senior members of the research team (Prof. Lesley Stewart and Prof. Stephen Palmer) to review methodological approaches, timescales, progress and outputs.

The key risk to the project would be an inability to obtain IPD for the existing studies. However as stated above, we have already secured agreement to collaborate from the authors of 16 studies. Our progress to date in securing agreement for a significant number of studies makes us confident that we will be successful in achieving this collaboration.

Ethical approval

Based on previous experience we do not anticipate that formal ethical approval will be required for the IPD meta-analysis as the secondary data to be used will have no identifying name or number and the project will be addressing the same clinical questions as the original studies to which the study participants consented. Data will be held securely in a password-protected area with access restricted to the project team. An application for exemption will be made to the University of York Health Sciences Research Governance Committee.

Patient and public involvement

PPI involvement in the proposed study will be mainly through our study expert advisory group (see below regards membership of the expert advisory group) and a consultation process with key stakeholders. This process has been informed by our previous work and the advice of our collaborators.

Expert Advisory Group

We will hold three half-day advisory group meetings to capture the perspectives of people with ASD, their carers, family, and local service providers in the proposed work. PPI representation on the advisory group will consist of five individuals, including a representative from the National Autistic Society (NAS) (Dr. Judith Brown), two parents of people with ASD (Anne McLaren and Elaine Walker), and two people with ASD. The rest of the advisory group will include an experienced clinician (Dr. Dean McMillan), an educational psychologist (Dr. Emma Truelove), an academic professional in the field (Prof. Patricia Howlin) and a teaching assistant with experience of delivering interventions to children with ASD in primary schools.

All members of the advisory group will be given a pack with terms of reference for the group. These will detail the purpose and responsibilities of this group as well as the membership of the advisory group as a whole. The terms of reference will also detail how the group will work, how often meetings will be held and how the members can feed back to the researchers outside of official meetings. In the first meeting we will provide training on the purpose and nature of systematic reviews and what we will be doing in our project. Group members will be asked about any pre-existing beliefs they may have about the effectiveness and provision of ABA-based therapies before

the first meeting. If possible, we will attempt to include a range of views on ABA-based therapy within the group. It will be explained to all members that the aim of the project is to provide an evaluation of the available evidence, including any areas of uncertainty. Though all members will be free to express their opinions and discuss the implications of the research, it will be made clear that the research itself aims to be objective and impartial.

Prior to the first meeting of the expert advisory group, we will contact all members to identify whether they have any particular social-communication or sensory requirements. To further facilitate the contribution of all advisory group members we will set out clear ground rules within the meetings. We will also ask for feedback from all group members involved in the meetings on whether they have any suggestions for improvement for future meetings. Feedback on any recommendations or outcomes, which arise from the meetings, will be shared with group members through plain English summaries or using their preferred form of communication. It is however possible that due to the social and communication difficulties experienced by individuals with ASD that some PPI members might find it difficult to attend or express themselves in some of these meetings. As far as is practicable individualised social communication adjustments will be made (e.g. use of Skype, email, telephone conference call facilities) and opportunities to prepare for meetings or supplementary meetings with individual members will be undertaken to ensure that their views are captured.

Parents/carers and adults with ASD attending the expert advisory group will be compensated for their time in accordance with INVOLVE rates and will be compensated for any costs associated with attending the meeting.

The expert advisory group will be involved in a number of aspects of the proposed research these are outlined in more detail below.

Design and conduct of the research

As outlined above we will hold three half-day expert advisory group meetings dedicated to capturing the perspectives of experts by experience (people with ASD, parents/carers , families) and a range of professionals (local service providers, clinicians and academics involved in the field). Advisory group meetings will be chaired by either Robert Hodgson or Mark Rodgers and each meeting will be structured to ensure each PPI member has the opportunity to contribute. Each half-day meeting will have specific objectives:

- The first meeting will seek to discuss and request comments on the project protocol, this will include, but not be limited to help in identifying/ any relevant baseline characteristics that we have not captured that would be important to include for the final analysis of effectiveness; identifying what outcomes are important to children and adults with ASD and their families; defining the nature of individual ABA-based treatments and if there are any treatments that we have not listed that may meet inclusion criteria; developing and refining a taxonomy of ABA-based treatments to inform decisions about subgroup analysis and data synthesis; and, identification of search terms.
- The second meeting will seek to aid the research team in the design of the economic model, to ensure that it captures key elements of the condition and has face validity. This will include, but not be limited to help in identifying current care pathways and service provision in the UK, identification of the quality of life benefits resulting from improved clinical outcomes; and identification of important secondary outcomes beyond costs and QALYs (for example independent living).
- At the final advisory group meeting we will present the results of our study and involve parents and adults with ASD in evaluating the key findings in terms of their meaningfulness to the everyday lived experiences families and children with ASD. These views will then be captured and reflected in the final report. We will obtain input on the summaries that will form part the final report and in particular the Plain English summary to ensure that it is accessible and meaningful to people with ASD and their carers.

In addition to the above, expert advisory group members will also have the opportunity of direct communication through their preferred method of communication (Skype, email/telephone). Where

appropriate, one or two representatives from the expert advisory group may also be invited to attend specific research team meetings. The views of all members of the expert advisory group will inform the project. Final responsibility for the research including decisions about the conduct of the study and the interpretation of the findings rests with the research team.

Analysis and interpretation of the results

The expert advisory group will not be directly included in the handling of data or completion of the analyses. We do wish however to include them in the interpretation of the results at an early stage. The results of the study will be circulated prior to the final expert advisory group meeting. This meeting will focus on potential interpretations of these results and how well they fit within the economic model. PPI members and the clinical and academic members of the expert advisory group will specifically be asked to consider how the results might be interpreted in the current UK context.

Contributing to reporting of the research

Advisory group members who wish to comment on drafts of the final report will be included in the circulation list and invited to comment on any document via email or if preferred on hardcopies sent to their address.

Dissemination of research findings

We will ensure that the project results are accessible to all relevant stakeholders including people with ASD and their carers. Advice will be sought from the expert advisory group about important local and national outlets that can be used to disseminate findings in an accessible format. PPI members will also be asked to contribute to and review a plain language 'evidence briefing' paper for dissemination to non-research audiences. Where appropriate, advisory group members' social media networks will be used to further disseminate the research findings.

Consultation process

In additional to the expert advisory group outlined above, we will also seek wider stakeholder input via a consultation stage whereby relevant stakeholder groups and organisations not otherwise represented on the expert advisory group will be invited to comment on the draft version of the final project report. Such organisations will be provided with the aims and terms of the consultation alongside a pro forma on which to provide comments. A maximum of one set of comments will be accepted from each stakeholder organisation, and organisations will be permitted to submit a joint response. Stakeholder comments will be used by the project team to inform the interpretation and wider discussion of the evidence in the final report. While comments will not receive individual separate responses, the full set of consultation comments will be made available alongside the final report for transparency.

Relevant organisations will be identified following consultation with our advisory and will be contacted directly to ensure that the number of organisations participating in the consultation phase remains feasible.

Expertise and justification of support required

Project base

The research project team is a multi-disciplinary partnership between Bristol, Newcastle and York Universities, with advisory input from National Autistic Society (NAS).

The Research Institute for Health & Society at Newcastle University has a history of undertaking the high quality research in neuroscience that translates into patient benefit, real world application and commercial opportunity. Their research focuses on health and welfare, public policy and practice with especial regard for developing guidelines for diagnosis and treatment; society and culture. In the recent 2014 Research Excellence Framework the majority of the institute's research activity was rated 4* indicating quality that is world-leading in terms of originality, significance and rigour.

The CRD is an academic department of the University of York that specialises in evidence synthesis. CRD regularly undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of care. The Centre hosts an NIHR Technology Assessment Reviews (TAR) team, an NIHR Health Services and Delivery Research Evidence Synthesis Centre, a Cochrane Programme Grant, the Cochrane Common Mental Disorders Group, and partners in the Policy Research Programme Policy Reviews Facility. In the 2014 UK Research Excellence Framework, the University of York - CRD, the Centre for Health Economics (CHE), the Department of Health Sciences and the Hull York Medical School (HYMS) - was ranked joint first for research environment in the Public Health, Health Services and Primary Care unit of assessment.

The Centre for Health Economics (CHE) was established at the University of York in 1983, and was one of the world's first research institutes dedicated to the study of the economics of health and health care. It rapidly established a leading international reputation, and is now one of the world's largest health economics research centres. In 2007 the University of York was awarded the Queen's Anniversary Prize for Higher and Further Education, in recognition of the contribution health economics research has made to the way society thinks about health and health care over the last 25 years. CHE has extensive expertise in decision-analytic methods for cost-effectiveness analysis, the use of evidence synthesis techniques and VOI to inform policy decisions in health and social care.

The School of Social and Community Medicine (SSCM) is one of the UK's leading centres for research and teaching in population health sciences. The School hosts the MRC Integrative Epidemiology Unit which is the MRC's flagship Unit leading the development of causal analysis methods. The School also hosts the NIHR School of Public Health, the NIHR School of Primary Care, the Centre for Academic Mental Health, the Centre for Child and Adolescent Health and the Centre for Research Synthesis and Decision-Making. The School's research was recognized as world leading in the 2014 Research Excellence Framework, with 100% of the impact activity rated as 4*, the only institution in this Unit of Assessment to attain this outstanding level of recognition.

The multidisciplinary team brings together expertise in systematic reviews, meta-analysis, decision modelling, and health technology assessment with relevant clinical expertise. Two clinical advisors have been included and costed in our proposal because development of the structure for the economic model and its parameterisation will require a range of expertise and perspectives including the experiences of both children and adults with ASD. Our advisory group brings broad range of expertise and includes patients' and carer's, as well a representative from the NAS, and number of clinical experts including an education psychologist, clinical psychiatrist and Academic clinical expert. This broad range of experience will provide a range of perspectives on the needs of people with ASD and the challenges of implementing early intensive ABA-based interventions in the UK

Expertise in the project team

Professor Ann Le Couteur is the Professor of Child and Adolescent Psychiatry at Newcastle University and honorary consultant at Northumberland, Tyne & Wear NHS Trust. She co-leads a multidisciplinary research team. ASD research themes include development and evaluation of diagnostic assessment and outcome measures (recently completed HTA review of outcome measures in young children with ASD and ongoing MRC study of use of ASD diagnostic tools in deaf children and young people); development and evaluation of early interventions for young children with ASD (MRC and NIHR RfPB) and treatment of co-morbidities (RfPB); experiences of transition in young people with complex long term healthcare needs including ASD (NIHR programme grant) and life course experiences of adults with ASD (Autistica). Le Couteur is an Associate editor for the Journal of Autism and Developmental Disorders, was one of the original authors of the Autism Diagnostic Interview; previous Chair of UK Association of Child and Adolescent Mental Health, an expert advisor for NICE and was a member of the GDGs for both ASD NICE clinical guidelines for children and young people .

Dr Dheeraj Rai is a senior lecturer in psychiatry at the University of Bristol and an honorary consultant psychiatrist at the Bristol autism spectrum service. He has clinical experience of working with individuals with autism across the life span and across the range of cognitive ability. He has a

strong track record of epidemiological research on the antecedents and outcomes of autism, and is also carrying out research on the feasibility of a guided self-help intervention for depression in adults with autism. He will provide clinical expert advice, inputting on all stages of the project and comment on the protocol and final report.

Dr Robert Hodgson is a Research Fellow in health economics and leads the health economics group in the CRD at the University of York. He is an experienced health economist who has worked in both academia and consultancy, with considerable expertise in both decision modelling and evidence synthesis. Robert's health economics experience includes the development of decision models for a variety of purposes including for projects for public health England and for private sector clients including the development of economic models as part of NICE technology appraisal submissions. He will lead the will co-lead the project and will lead on the cost-effectiveness analysis.

Dr Claire Rothery is a Senior Research Fellow at the CHE, University of York. Claire's research interests are centred on the application of statistical and decision-analytic methods for cost-effectiveness analysis and VOI to inform policy decisions in health care. Claire has worked on economic evaluations for over 10 years and was a member of the NICE Technology Appraisal Committee between 2013 and 2016. Claire is a leading expert in value of information analysis and is currently co-chairing the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Emerging Good Practices Guidance on value of information analysis for research decisions. Claire will provide advice and support on the cost-effectiveness analysis and lead the VOI analysis.

Mark Rodgers is a Research Fellow at the CRD, University of York. He has is an expert in Health Technology Assessment and evidence synthesis, with 15 years' experience. He has extensive experience in leading similar projects and has a long-standing research interest in the methodologies of systematic reviews and evidence syntheses. He is a standing member of NICE Clinical Guidelines Update Committee B and is an Associate Editor of the BMC journal Systematic Reviews. His role will have a particular focus on the methodological aspects of the proposed systematic review work.

Dr Mousumi Biswas is a Research Fellow in Health Economics at the CRD, University of York and contributing to health economic and quantitative synthesis components of CRD projects. She has extensive experience in evidence synthesis including meta-analysis using Bayesian statistical methods and economic evaluation of healthcare interventions particularly screening and monitoring for chronic health conditions. She recently contributed to a Health Technology Assessment (HTA) funded project on monitoring heart failure in primary and secondary care and NIHR funded project on natural history and prospect of early cancer diagnosis (Discovery Programme). Mousumi will contribute to all aspects of the economic evaluation.

Dr Mark Simmonds is an experienced medical statistician with particular expertise and interest in statistical methodology relating to meta-analysis, and in particular to IPD meta-analysis. He has been working in this area for 15 years and was one of the first people to complete a PhD on hierarchical modelling for IPD meta-analysis, and developed the concepts of one and two-stage meta-analysis. He has substantial research experience in IPD meta-analysis, heterogeneity estimation, survival analysis and hierarchical models for meta-analysis. Recent practical experience includes performing IPD analyses in spinal fusion surgery and in the epidemiology of gestational diabetes. He will design and run the complex syntheses and supervise the work of other statistician working on the project.

Dr David Marshall is a Research Fellow for Evidence Synthesis within CRD and completed his doctorate on attentional disengagement and interest in children with ASD. He has experience conducting systematic reviews and worked as a trial coordinator for an NIHR-funded study examining Social Stories for children with ASD. He worked for 2 years as an ABA teacher for children with ASD. David is currently a named collaborator on two NIHR funded grants: one looking at interventions targeting childhood phobias (HTA 15/38/04) and one investigating the effectiveness of LEGO-based therapy for children with ASD (PHR 15/49/32). David will contribute to all systematic reviews undertaken as part of the project.

Professor Lesley Stewart is Director of CRD. Her research interests are in the development and application of evidence synthesis methods, particularly for IPD meta-analysis. With colleagues, she

helped establish the methodology and framework for IPD meta-analysis, has completed many such international collaborative projects and published widely in the field. She was a founding member of the Cochrane Collaboration, has co-convened the IPD Meta-analysis Methods Group since inception, and chairs the PRISMA-IPD Steering Group. She is Co-Editor in Chief of the BMC journal Systematic Reviews, a member of the NICE Highly Specialised Technologies Evaluation Committee and has served previously as elected President of the international Society for Research Synthesis Methods. Lesley will provide expertise and advice on the IPD meta-analysis and will mentor and support team members in managing the project.

Professor Stephen Palmer is a Professor and Deputy Director of the economic evaluation team in CHE. He has worked in economic evaluation for over 20 years in areas including pharmaceuticals, cardiology, cancer, mental health, diagnostic and screening programmes and policy. He has extensive experience of economic evaluation (including inter-sectoral analyses), regulatory and reimbursement processes. He has worked closely with policy makers and currently leads the programme of work at CHE for the NICE. He is also a member of the NICE Decision Support Unit. Stephen will provide health economics support and advice throughout all stages of the project, as well as mentoring and supporting team members in in managing the project.

Expertise in the Advisory Group

In addition to the applicants named above the research will also be informed by the views of an advisory board, which will comprise of:

Carol Povey is Director of the Centre for Autism at the National Autistic Society, the leading UK charity for people with ASD and their families.

Dr Dean McMillan is a health services researcher and clinical psychologist with further specialist training in CBT. He is a co-applicant on a number of NIHR-funded trials of psychosocial interventions (e.g., CASPER, CASPER PLUS, COBRA, OCTET) and will bring expertise in the trial evaluation of psychological and behavioural interventions.

Prof Patricia Howlin is a Professor of Clinical Child Psychology at the Institute of Psychiatry, London, whose principal research interests focus on autism and developmental disorders including Williams syndrome, developmental language disorders and Fragile X. Howlin is a Fellow of the British Psychological Society, who has served as Chair of the UK Association of Child Psychology and Psychiatry and the Society for the Study of Behavioural Phenotypes She is a founding editor of the journal Autism. She is an expert in this field and was the lead author on a prominent review of EIBI in children with ASD.

Prof. Helen McConachie is a Professor of Child Clinical Psychology in the Institute for Health and Society and the University of Newcastle upon Tyne. Her principal research interests focus on children with disabilities (including ASD) and their families and she has led several studies evaluating and assessing appropriate outcome measures in children with ASD.

Prof. Mike Clarke is Director of the MRC Methodology Hub at School of Medicine, Dentistry and Biomedical Sciences, Queens University Belfast, Director of the Northern Ireland Clinical Trials Unit and the Northern Ireland Methodology Hub, and Co-coordinating Editor of the Cochrane Methodology Review Group. His research focuses on the evaluation of the effects of health and social care interventions and he has contributed to numerous randomised trials, systematic reviews and other prospective studies including a number of individual participant data systematic reviews/meta-analyses.

Dr Emma Truelove is an educational psychologist and autism link as part of the Educational Psychology Service in York. She works with children and young people aged 3 to 25, their parents and carers and a wide range of other professionals. The aim of the service is to promote the wellbeing, personal development and education of children through the application of psychology in providing consultation, assessment, advice, and interventions.

Anne McLaren is a parent of a child with ASD in York. She has contributed as a PPI representative to the application, design, management and dissemination of material in the Autism Spectrum Social

Stories In Schools Trial (ASSSIST) including the systematic review completed as part of this project. She also was a member of the writing group for the development of a Social Stories manual and a contributor to the book Uncut Cords: Caring for Our Sons and Daughters with Learning Disabilities.

Emma Jenner is a parent of a teenage boy with ASD in York. She was involved as a participant in ASSSIST study and is a member of the PPI panel for a recently funded trial examining LEGO therapy for children with ASD (PHR: 15/49/32).

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Department of Health disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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Appendix 1 –Draft Search Strategy

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 Child Development Disorders, Pervasive/ (6729)

2 Autistic Disorder/ (17989)

3 Autism spectrum Disorder/ (1289)

4 Asperger Syndrome/ (1638)

5 1 or 2 or 3 or 4 (25723)

6 (pervasive development$ disorder$ or PDD or PDDs).ti,ab. (4045)

7 (ASD or autistic or ASD or ASDs or ASC or AAC).ti,ab. (46624)

8 Asperger$.ti,ab. (1900)

9 Kanner$.ti,ab. (189)

10 Rett Syndrome/ (2143)

11 (rett or retts).ti,ab. (3004)

12 Intellectual Disability/ (50213)

13 Developmental Disability/ (17141)

14 Communication Disorders/ (1868)

15 Speech Disorders/ (10590)

16 Language Development Disorders/ (5440)

17 ((communicat$ or speech or language) adj2 (delay$ or disorder$)).ti,ab. (9297)

18 Child Behavior Disorders/ (19303)

19 (child$ adj2 behavio$ disorder$).ti,ab. (781)

20 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (151855)

21 "Early Intervention (Education)"/ (2236)

22 Behavior Therapy/ (25227)

23 (intensive$ adj2 (analys$ or behavior$ or behaviour$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (24227)

24 (intensity adj2 (analys$ or behavior$ or behaviour$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (7157)

25 (high-intensity adj2 (analys$ or behavior$ or behaviour$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (881)

26 (low-intensity adj2 (analys$ or behavior$ or behaviour$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (957)

27 (high intensity adj2 (analys$ or behavior$ or behaviour$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (881)

28 (low intensity adj2 (analys$ or behavior$ or behaviour$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (957)

29 (intensive behavior$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (210)

30 (intensive behaviour$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (48)

31 (early behavior$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (34)

32 (early behaviour$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (10)

33 (comprehensive behavior$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (101)

34 (comprehensive behaviour$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (12)

35 (applied behavior$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (384)

36 (applied behaviour$ adj2 (analys$ or intervention$ or program$ or therap$ or treat$)).ti,ab. (36)

37 (IBI or EIBI or ABA).ti,ab. (9227)

38 Lovaas$.ti,ab. (35)

39 (Early Start Denver Model or Denver Model).ti,ab. (28)

40 (ESDM or ESDM-I or ESDM-PD or P-ESDM).ti,ab. (27)

41 (Pivotal Response adj2 (treat$ or train$ or program$)).ti,ab. (42)

42 (PRT train$ or PRT program$).ti,ab. (43)

43 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (67835)

44 20 and 43 (4634)

45 Infant/ (712134)

46 exp Child/ (1705358)

47 (baby or babies or child$ or infant$ or infancy or boy or boys or girl or girls or kindergarten or nursery or pre-school$ or preschool$ or toddler$).ti,ab. (1561159)

48 45 or 46 or 47 (2480423)

49 44 and 48 (3631)