REACH-ASD Trial: A Randomised Controlled Trial of Psycho-Education and Acceptance & Commitment Therapy for Parents of Children recently diagnosed with ASD

Trial Protocol

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Pennine Care NHS Foundation Trust
KING'S College LONDON
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A Randomised Controlled Trial of Psycho-Education and Acceptance & Commitment Therapy for Parents of Children recently diagnosed with ASD (REACH-ASD)

CONTENTS

1. GENERAL INFORMATION

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Start date:	01/09/2019
Duration:	42 months

2. AMENDMENTS

2.1 Protocol Amendments

The following changes have been made to the protocol.

Old Version	*New version*	*Date*	*Amendment*
0.4	**1**	**17.12.2019**	Addition of 3 questionnaires – Subthreshold autism traits questionnaire; Acceptance and Action Questionnaire-2; The Reaction to Diagnosis Questionnaire.
1	**2**	**01.04.2020**	Due to the COVID-19 pandemic, adjustments to research visits have been made. It is now possible for baseline, and weeks-12, -26 and -52 visits to also be completed remotely so that researchers do not physically have to see participants. They have the option to use post, email, online surveys, phone, videoconferencing etc.

2.2 Amendments submitted to NHS Research Ethics Committee/HRA and/or Trial Sponsor

Number of amendment	*Relates to Protocol Amendment dated*	*REC/HRA Approval date*
Substantial Amendment 1	17.12.2019	13.02.2020
Minor Amendment 2	01.04.2020	06.04.2020 (Sponsor approval only required)

3. COLLABORATORS

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4. TRIAL SUMMARY

4.1 Objectives
To evaluate the EMPOWER-ASD intervention, a parental group-based manualised post-diagnostic programme that combines ASD psychoeducation and a brief Acceptance and Commitment Therapy: (1) To complete testing of acceptability, qualitative analysis and finalisation of the programme (feasibility phase); (2) To complete an implementation process evaluation; (3) To test intervention effectiveness over treatment as usual (TAU) on: (a) parental mental health, wellbeing, knowledge, adjustment, stress and self-efficacy; (b) family wellbeing, (c) child wellbeing, behaviour and adaptive functioning; (4) To assess its cost-effectiveness.

4.2 Design
A multi-centre two parallel group single (researcher)-blinded randomised controlled trial of the EMPOWER-ASD programme plus TAU versus TAU alone. Individual randomisation by child, with one “index” parent per child, and stratification by centre, using 2:1 randomisation ratio to assist recruitment and deliver timely intervention. Initial feasibility phase and internal pilot to test recruitment, both with pre-specified progression criteria. Population: parents/primary carers of children and young people aged 2-15 years with a recent ASD diagnosis. Primary outcome: parental mental health (General Health Questionnaire- 30) at 52-week follow-up. Secondary outcomes: key parent measures at 12-, 26- and 52-week follow-up and family and child outcomes at 52-week endpoint. Sample: N=330 (220 intervention/110 TAU).

4.3 Analysis
Primary analysis will follow intention-to-treat principles. Treatment effects will be analysed using linear mixed models with random intercepts for group membership. Cost-effectiveness acceptability analyses over 52 weeks, with decision modelling to extrapolate to longer time periods.

4.4 Participants
Participants are parents/primary caregivers of children aged 2-15 years with a recent ASD diagnosis recruited from 6 Greater Manchester NHS centres.

4.5 Intervention
The EMPOWER-ASD intervention is a parental group-based manualised post-diagnostic programme that combines ASD psychoeducation and a brief Acceptance and Commitment Therapy (ACT). The ASD psychoeducation includes: an introduction to ASD; strategies to support understanding and communication; understanding and managing emotions, behaviour and sensory needs, and navigating the education system. The ACT elements provide psychological input to parents to support their mental health, stress management and adjustment to their child’s diagnosis. The intervention will be delivered by trial-specific NHS practitioners alongside local specialist clinicians. Treatment-as-usual is variable across collaborating centres and will be specified through health economic data.

5. BACKGROUND

5.1 Health need

Autism Spectrum Disorder (ASD) is a lifelong neurodevelopmental condition affecting over 1% of UK children, usually diagnosed from about 3 years, and defined by impairments in social reciprocity, communication and restricted, repetitive patterns of behaviour, interests, or activities. The impact of these clinical features is variable across individuals, but often bears a profound influence on development, functioning and wellbeing into adulthood. Given the enduring developmental nature of ASD, intervention strategies need to be considered at different phases of the disorder. Following diagnosis, current evidence supports the effectiveness of some specific pre-school intervention strategies on dyadic parent-child interaction and on child autism impairments.[1,2] However, provision in the immediate post-diagnostic period remains un-evidenced. This period can present real challenges in adaptation for families, as well as being their first introduction to service provision in the area. The incidence of clinically significant parental mental health need around this time is 20-50%.[3,4] Responses to the diagnosis are heterogeneous: feelings of grief, disorientation and disempowerment are common.[5,6,7] Some parents feel relief; others are strongly motivated to seek out information and support so guidance in how to access high-quality evidence-based information is paramount. Such parental needs are of public health importance in and of themselves. In addition, improved parent wellbeing is likely to have downstream effects on family and child wellbeing, plus will result in more effective uptake of subsequent evidenced-based parent-mediated interventions known to bring long-term benefits for both the parent and the child with ASD.

Best practice guidelines[8,9,10] recommend provision of timely post-diagnostic family support. However, current provision is patchy across the UK,[5] a source of increasing dissatisfaction for both parents and professionals;[11,12,13,14] and crucially, it, lacks any evidence-base for effectiveness. There is therefore a pressing need for an evidenced programme of post-diagnostic support for parents, focussed on parental mental health and adaptation.[11,12,15] Prior theory, evidence and parent consultation indicate that such support should combine ASD psychoeducation along with psychological strategies focused on parental adjustment and wellbeing. Each of these components in combination will contribute to improved parental mental health.

5.2 Current evidence

5.2.1 Post diagnostic psychoeducation

There is no formal evidence base for a parental post-diagnostic ASD psychoeducation within the UK. Observational studies suggest preliminary support of manualised psychoeducation programmes, like ASCEND[16] and Cygnet[17] and anecdotal clinical reports are of good acceptance. Internationally there have been a small number of RCTs of psychoeducation with generic/child outcomes[18,19] and one RCT with a treatment effect on parental mental health.[20]

5.2.3 Post diagnostic psychological intervention

Cognitive-behavioural approaches have been applied to parents of children with ASD, with some promising results.[21] However, a problem-solving

approach alone may not be specific enough to address the distinct psychological task faced by these parents. Acceptance and Commitment Therapy (ACT)[22] has a growing evidence base for effectiveness in adult mental health.[23,24] ACT shares lineage with cognitive-behavioural interventions and shows similar general effectiveness.[23] ACT holds particular relevance to this task due to: i) its emphasis on psychological acceptance (validating challenging emotions and cognitions, rather than seeking to change them);[25] ii) incorporation of mindfulness techniques (successful in reducing parental and child psychopathology)[26,27] but in a way that is more sustainable than full mindfulness interventions that have high time and training costs;[28] iii) a ' core values' focus that may help parents re-assert parenting values challenged by realisation of the child's condition.[28,29] Early evidence supporting ACT in ASD to improve parental mental health includes a small-scale RCT (N=18)[30] comparing a 4-hour ACT programme against no intervention and reporting a large effect on parental depression (d=-1.01) and three small-scale (N=20-33) observational studies reporting improvements in parental depression and parenting stress.[25,31,32] An RCT of a 5-hour ACT programme as part of a package for parents of children with Acquired Brain Injury compared to TAU (N=59)[33] found moderate effects on parental stress (d=0.56), anxiety (0.39) and parenting confidence (0.67). The same ACT programme then showed good applicability and acceptability when applied post-diagnostically with groups of parents of children with ASD, with very positive qualitative feedback (Sofranoff, pers comm).

5.2.4 New knowledge

This trial tests a brief psychosocial intervention which directly addresses the identified health need. The EMPOWER-ASD programme has been developed from existing practice, theory and service-user collaboration; it is deliverable within the NHS, and aims to address the mental health needs of parents of children with ASD through integrating problem-focused psychoeducation and a brief manualised ACT therapy within a short group-based programme. If shown to be effective, this theoretically based targeted approach to parental education, empowerment and stress reduction will fill a key evidential gap in the provision of efficient and effective developmentally sequenced ASD interventions from diagnosis onwards.

5.3 Necessity for this research (in terms of time and relevance)

There has been a recent step change in identifying effective episodic interventions for early autism within robust RCTs. CI Green and colleagues have been frontrunners in this progress: our UK MRC-funded trial of Pre-school Autism Communication Therapy (PACT)[2] is the first to show a long-term reduction in autism symptoms, 6 years after a pre-school treatment, and our infancy prevention trial (iBASIS)[34] the first to show a similar medium-term reduction in prodromal ASD symptomology in infants at familial risk of ASD. Despite these significant developments, there are still large gaps in our understanding of what constitutes an effective pathway of sequential developmentally phased interventions for ASD.[35] Post-diagnostic psycho-social intervention for parents has received relatively little research attention and remains a large evidence gap, not only in the UK context but internationally, in spite of parental psychoeducation being amongst the most commonly used ASD interventions. There are local clinical initiatives to develop and

run psychoeducation packages but very few have been subject to rigorous testing. The Manchester Psychoeducation Workshop approach is an example of this and with over 10 years' development work and proof-of-concept, an RCT of its effectiveness is overdue.

In parallel to developments in the ASD field, there have been recent advances to psycho-therapeutic approaches to mental health conditions, like depression and anxiety, with an increasing evidence base for third wave therapies like ACT. Several teams have now recognised the relevance of ACT to the parental post-diagnostic ASD context, with three observational studies[25,31,32] and one small-scale RCT (N=18)[30] pointing to preliminary effectiveness. The emphasis on the health and wellbeing needs of the adults (parents) involved with children with ASD is an important one. The EMPOWER-ASD programme meets these needs at two levels: (i) educational support to enable their empowerment through knowledge of the disorder and their ability to make informed and positive choices for ongoing care; (ii) psychological support with the immediate challenge parents face in adjusting to a serious diagnosis in their child with long-term implications.

REACH-ASD will be conducted in accordance with the principles of GCP and applicable UK regulatory requirements.

6. OBJECTIVES

Aim
To evaluate the effectiveness and cost-effectiveness of the EMPOWER-ASD intervention: a parental group-based post-diagnostic programme that combines ASD psychoeducation with focussed psychological support to improve parental mental health.

Objective 1
To complete intervention co-design with practitioners and two groups of parents: testing of acceptability and feasibility through satisfaction ratings and qualitative evaluation, and modification and finalisation of intervention manual (feasibility phase)

Objective 2
To identify perceptions of the intervention and barriers to implementation within routine service provision (process evaluation in main trial)

Objective 3
To test the effectiveness of the EMPOWER-ASD intervention over usual care on (i) parental mental health (primary outcome) (ii) parental knowledge, wellbeing, health status, and adjustment, and (iii) parenting stress and self-efficacy, at 12, 26- and 52-week follow-up

Objective 4
To test the effect of the intervention on: (i) family wellbeing; and (ii) child wellbeing, behaviour and adaptive functioning at 52-week endpoint

Objective 5
To assess the: (i) net costs and quality adjusted life years (QALYs) of the intervention compared to TAU and whether, when compared to TAU, the intervention is cost-effective (primary analysis); (ii) cost-effectiveness of the intervention using measures of parental mental health and child wellbeing (sensitivity analysis)

7. DESIGN

A multi-centre two parallel group single (researcher)-blinded randomised controlled trial of the EMPOWER-ASD intervention plus TAU versus TAU alone, for parents/primary caregivers of children aged 2-15 years who have received an ASD diagnosis within the previous 12 months, with parental mental health (General Health Questionnaire-30; GHQ-30) at 1-year follow-up as the primary outcome, key parent, family and child secondary outcomes, cost-effectiveness analysis and a nested process evaluation.

7.1 Primary Outcome
Parental mental health, measured by the General Health Questionnaire-30 (GHQ-30),[46] measured at baseline and 12-, 26- and 52-week follow-up.

The GHQ is the gold standard self-report measure of mental health in the general population or within community/non-psychiatric clinical settings. It is widely used in mental health trials, is well-validated and has excellent sensitivity to change and psychometric properties, yielding normally distributed data.[46] There is no well-validated *blinded* measure of parental mental health for use within clinical trials. The GHQ is appropriate to measure mental health needs this context, in which parents are epidemiologically at risk but are not themselves selected on the basis of a mental health diagnosis. It will be, therefore, more sensitive to change than other screens/diagnostic tools designed for psychiatric populations, such as the WHO-SCAN or the MINI. It provides a unitary measure of symptoms of both depression and anxiety (other instruments like the MADRS and GAD-7 focus on one or the other). It assesses current mental state, rather than long-standing attributes of the respondent, and is therefore suited to measuring shorter term change that may be influenced by the child's recent diagnosis. The GHQ has been successfully used to show a treatment effect on mental health in parents of children with ASD in several previous studies,[47] including an RCT of a psychoeducation group[20] and an observational study of ACT.[25]

The GHQ-30 is the most widely validated version of the GHQ with over 29 validity studies (GHQ User's Guide, 1988, p.21). It yields an overall total score to be used as the primary outcome. It was developed from the GHQ-60 but takes half the time to complete (3-4 mins as opposed to 6-8 mins) – important when participants will be completing several questionnaires at multiple time points. At an item level, the GHQ-30 is more appropriate than the GHQ-28 to administer to this non-clinical patient group (e.g., fewer items on suicidality). The GHQ-30 has published clinical cut-offs so rates of caseness can be used to assess meaningful and clinically significant change alongside the total score as a measure of absolute change.

7.2 Secondary outcomes
Parent measures, measured at baseline and 12-, 26- and 52-week follow-up:

- Parental ASD knowledge (Autism Knowledge Questionnaire,[43,44,45] developed for current UK context)
- Parental wellbeing and quality of life, using the Warwick and Edinburgh Mental Wellbeing Scale WEMWBS;[48] a core outcome measure
- Parental Health Status EuroQol Five Dimensions Health Questionnaire, 5L version (EQ 5D-5L) - Self reported version[49]
- Parental adjustment to diagnosis (Reaction to Diagnosis Interview, RDI[50] and The Reaction to Diagnosis Questionnaire, RDQ[67])
- Parenting stress (Autism Parenting Stress Index, PSI)[51]
- Parenting self-efficacy (Tool to measure Parenting Self Efficacy, TOPSE)[52]
- Parental measure of subthreshold autism traits (Subthreshold Autism Questionnaire, SATQ)[68] – At 12-week only
- Parental flexibility (Acceptance and Action Questionnaire – II, AAQ-II)[69]

7.2.1 Family Measures, measured at baseline and 52-week endpoint

- Family wellbeing, by a parent-nominated self-report measure of family experience and wellbeing developed through parent consultation within our previous trials (Autism Family Experience Questionnaire, AFEQ)[53]
- Expressed Emotion as a blind-rated measure of family emotional climate (Autism Five Minute Speech Sample)[54]

7.2.2 Child Measures at baseline and 52-week endpoint

- Child adaptive functioning (parent- and teacher (blind)-rated Vineland Adaptive Behaviour Scales, VABS)[55]
- Child wellbeing and health status: parent-rated Child Health Utility-9D Index (CHU-9D), valued to allow calculation of QALYs[56]
- Child emotional and behaviour difficulties (parent- and teacher (blind)-rated Strengths and Difficulties Questionnaire, SDQ);[57]

7.3 Baseline measures

Demographics (including parent age and ethnicity, child age, family socio-economic status, number of people in the household, number and age of siblings, languages spoken), clinical information (date of child's ASD diagnosis, other child medical diagnoses, parental mental health or neurodevelopmental diagnoses; medical diagnoses of siblings), child autism severity (Social Communication Questionnaire, SCQ);[58] and adaptive behaviour (VABS) as a proxy for IQ.

7.4 Service use

Health and Social Care Service-Use Interview (SUI) at baseline, 26- and 52-week follow-up. The SUI will include questions about whether the parent and child have used any primary, secondary or community-based health and social care and how often they used the service in the last 3 months (baseline study visit) or since the last assessment (follow-up study visits). This will provide information about TAU for the 'index' parent and child with ASD within each family. The SUI will also include time spent by family as informal carers, use of other public services and time in paid and unpaid employment/productive activity. The SUI will be developed from existing ASD related SUIs held by the Co-applicants and through discussion with the PPI representative, parent advisory group and clinical members of the study team.

8. TRIAL INTERVENTION

8.1 Treatment as Usual (TAU)
Standard care pathways are specified[8,9] but vary considerably across services and NHS Trusts. Provision ranges from no follow-up care to one or more of: single session review; NHS or NGO-led group interventions; individual needs-led interventions; onward referral.[11] Feedback from clinicians gives similar patterns of variation within the Greater Manchester region. These centre differences will be captured via detailed service-use data collection and factored into the design and analyses by stratifying the randomisation by centre.

8.2 Experimental Treatment
The trial will assess the EMPOWER-ASD programme, a closed-group manualised intervention composed of 5 x 3-hour sessions. Ten index parents will attend each group (with one additional non-trial adult per family, if desired; group size: 10-20). The programme contains 3 components:

8.3 ASD Psychoeducation and Empowerment
A workshop model developed and delivered over 10 years by Hackett and colleagues within the Manchester University NHS Foundation Trust Child and Adolescent Mental Health Service (MFT CAMHS), the only UK CAMHS team rated as outstanding by the Care Quality Commission. The model uses collaborative problem-solving to skill up parents to become ASD experts. Themes include: (i) understanding ASD; (ii) understanding and working with the education system; (iii) enabling your child's communication and understanding; and (iv) understanding and managing behaviour and sensory issues (further detail provided in the programme protocol below). Parents are informed about evidence-based practice and directed to local, national and online sources of information and support. Published evaluations report excellent feasibility and acceptability.[36,37] Service evaluation of 2 groups run in 2017 (unpublished) showed that 15/16 parents found the group useful and 100% would recommend it.

8.4 Acceptance and Commitment Therapy (ACT)
The ACT component is a manualised 5-hour programme developed specifically for parents of children with disabilities,[33,38] used with the developers' consent. The sessions aim to develop psychological flexibility and promote stress reduction and adjustment through two main principles: *(i) Acceptance of those things beyond your control:* reflection on current struggles/stress surrounding the child's diagnosis/condition and existing strategies for dealing with this; the option of accepting these struggles/difficult thoughts and feelings rather than fighting against them; simple mindfulness techniques to deal with stressful situations, to become aware of own thoughts and feelings, and to choose whether or not to engage with them; *(ii) Commitment to making changes that are important to you and your family:* reflection on core parenting values (what really matters to each individual as a parent); the barriers in putting those values into action, particularly in light of the child's needs and recent diagnosis, and any possible solutions to overcome those barriers; making a commitment to moving towards one's core values. These two principles are introduced and reinforced through explanations, metaphors, videos, individual reflection and tasks, and group discussion, role play and experiential exercises.

8.5 Web-based Supplementary Resources
Participating parents will have access to a secure web portal developed during the pre-trial and start-up phase by IT services at The University of Manchester, in collaboration with Co-applicants, and hosted on the University server (no additional cost). This website will support programme-related content: videos of workshop presentations, including versions translated into community languages (already under development within MFT CAMHS); links to videos to support the ACT strategies; signposting to further ACT information and support for those who wish to learn more; signposting to existing highly-regarded databases of organisations and sources of support, such as the National Autistic Society forum and the Autism Speaks 100 day toolkit.

8.6 Integration of components
The EMPOWER-ASD manual will combine psychoeducation and ACT elements into an integrated group programme, with the key aim of improving overall parental mental health - as outlined in the protocol and logic model below. The precise details of the protocol will be refined in the feasibility phase through qualitative feedback and co-production with two groups of parents and practitioners and finalised prior to the pilot phase.

8.7 Delivery
Trial-specific NHS Practitioners will be recruited to deliver the EMPOWER-ASD programme, trained and supervised by Co-applicants Hackett and Dunkerley and an ACT Consultant. The Practitioners will be knowledgeable about ASD, experienced in running group-based interventions and skilled in both delivering didactic content and in facilitating group learning processes. Within each referral centre, local clinicians will work in collaboration with the Practitioners to offer session specific expertise and localisation. This delivery model was used successfully within the Manchester ASSIST Trial.[39] This approach will also build capability and sustainability within local teams.

8.8 Treatment Fidelity
Intervention sessions in the feasibility phase will be video-taped and reviewed by supervisors and the ACT consultant, as part of the training process. During the pilot and main trial, all sessions will be audiotaped, and a random sample of 10% of sessions will be assessed for fidelity to the manual by a fully-trained independent CAMHS practitioner and the ACT supervisor (their costs have been included). The core competency framework proposed by Luoma (2017)[40] will be used to formally rate fidelity and will be accessed throughout the study by the Practitioners to aid their self-assessment of adherence.

9. TRIAL PHASES AND PROGRESSION CRITERIA

9.1 5-month feasibility phase
We have already undertaken extensive clinical piloting of the psychoeducation components of the EMPOWER-ASD model in local areas and are therefore confident in its acceptability and feasibility. The ACT components have been piloted with parents with ASD by Sofranoff and Whittingham (pers. comm.), but would be new to the local context. The feasibility phase will focus on the feasibility and

acceptability of the more novel aspects of the intervention: the integration of the psychoeducation and ACT components within one programme; the use of ACT metaphors (abstract or concrete; feedback from Sofranoff and colleagues suggests parents with a Broader Autism Phenotype may struggle with more abstract metaphors); the usefulness of in- and between-session ACT practices; and the strategies for promoting peer support networks. The online resources are already under development and will reach completion in the start-up phase, and the feasibility phase will be used to assess the usability of these resources.

The full intervention package will be delivered by trial staff with local clinicians and 2 groups of 10 parents (recruited from 2 recruitments sites during start-up phase). Acceptability will be tested through uptake and parent satisfaction ratings collected by questionnaire at the end of each session (see progression criteria below).

Within these 2 feasibility groups, qualitative practitioner and parent feedback on details of delivery, accessibility and acceptability will be collected via (i) session-specific feedback forms and (ii) semi-structured focus groups and interviews following the last intervention session. These will be analysed and discussed with our parent advisory group, the trial team and the Trial Steering Committee (TSC) (see section 5.10 below for further details). Further co-design with practitioners and parents will inform the final intervention protocol, prior to the pilot phase.

Within the feasibility phase, the Research Associate and Assistant will train in and practise all research measures. The Trial Manager will work with the Clinical Trials Unit to set up the randomisation system and online database. Co-Applicant Leadbitter will finalise the Autism Knowledge Survey-Revised[41,42,43] (modified to reflect current UK ASD knowledge and practice and piloted pre-trial with parents recruited through the autism@manchester network as part of a Masters thesis).

Pre-specified criteria for progression: These will focus on acceptability as measured through group attendance and satisfaction ratings within 2 intervention groups of 10 parents, adopting a “traffic light” approach:

- *Green:* ≥ 70% of consented families attend ≥3/5 of the intervention sessions AND ≥70% of parental session-specific satisfaction ratings are “satisfied/very satisfied”. 3/5 sessions considered the minimum necessary dosage for clinical benefit from our experience. Satisfaction levels within Hackett’s clinical service are consistently >90%. The study will progress as planned.
- *Amber:* 50-69% of consented families attend ≥3/5 of the intervention sessions AND/OR 50-69% of satisfaction ratings are “satisfied/very satisfied”. The qualitative evaluation will be used to identify key problems, set strategies to address these and review at end of pilot phase.
- *Red*: <50% of families attend ≥3/5 of the intervention sessions AND/OR <50% of satisfaction ratings are “satisfied/very satisfied”. The TSC and the HTA Programme will advise on progression conditions with a view to trial termination, unless the qualitative analysis clearly identifies key problems that are rapidly and easily resolved.

9.2 4-month Internal Pilot Phase:
Test of randomised design and recruitment to the study in 4 centres, using the fully developed intervention package and a full assessment battery. Target recruitment n=60; 15/centre; 3.75/month/centre = same rate as required in main trial.

Pre-specified progression criteria (also adopting a traffic light approach): This will focus on sufficient recruitment to randomisation:

- *Green:* 15 parents randomised to trial pilot in 4 months in ≥3/4 centres. The main trial will continue as planned.
- *Amber:* 15 parents randomised to pilot in 4 months in 2 centres. We will identify key barriers to recruitment in discussion with the problematic centres and adopt measures to overcome these and, if issues are insurmountable, we will pursue substitute recruitment centres. Recruitment will be reviewed after a further 4 months and progression criteria re-applied.
- *Red:* 15 parents randomised in 4 months in <2 centres. The TSC and the HTA Programme will advise on progression conditions with a view to trial termination, unless the team can clearly identify barriers to recruitment that are rapidly and easily resolved.

9.3 24-month Main Trial:
Addition of 2 further recruitment centres (6 in total); over 12 months to recruit and randomise additional 270 participants from 6 centres (45/centre; 3.75/month/centre). 3 intervention groups per centre/year, with 10 participants per group. Baseline and 12-, 26- and 52-week outcome assessments completed with minimal loss to follow-up.

9.4 Nested qualitative process evaluation
During the final six months of the main trial we will undertake a qualitative process evaluation, led by Co-applicant Bee. It will draw on recognised theoretical frameworks to analyse intervention acceptability (Theoretical Framework of Acceptability)[44] and inform intervention development, implementation and sustainability (Normalisation Process Theory)[45]. This will take patient and practitioner perspectives on tasks relevant to the implementation of the intervention using constructs of: a) Coherence - how people understand and make sense of a novel intervention and its potential benefits relative to what is currently available; b) Cognitive participation – its face validity; c) Collective action – requirements for implementation including fit with existing skills and practices; d) Reflexive monitoring - how the new intervention is appraised, in terms of benefits against additional work required. We will collect data from multiple informants (n=30). We will include participating parents from both trial arms (n=15), as well as those disengaging from the intervention (n=5). Purposive sampling will ensure data is representative of the wider demographic. Semi-structured interviews will elicit descriptions of how parents have perceived and understood the intervention and how it has or has not been applied and embedded into their lives, including exploration of its most and least helpful components. We will also interview co-delivering clinicians and service team members (n=5) and supplement these with key informant interviews (service commissioners, policy-makers, national ASD and third-sector leads; n=5) to give understanding of the broader organisational and systems contexts that may impact on intervention sustainability and roll out.

10. HEALTH ECONOMICS

A detailed economics analysis plan will be approved by the DMEC and TSC prior to analysis of follow-up data. The analysis plan will be informed by published literature supplemented with descriptive analysis of pooled (unblinded) baseline data to identify key covariates for imputation and regression models for the follow up data. The economic analysis will use a within-trial, intent to treat approach and include all participants randomised to the two trial arms. The primary analysis will use the NHS and Social care (costs) and parents/primary caregivers (health benefits) perspectives, with a 12 month time horizon.

Costs will be estimated from a Service-Use Interview (SUI) at baseline, 26- and 52-week follow-up (health and social care service use). When the data are analysed, the most recent, published, national unit costs will be used to cost each of the services used (PSSRU Unit Costs of Health and Social Care; Department of Health Reference Costs).[61,62] The SUI will produce data on informal care costs, use of other public services, and time in paid and unpaid employment/productive activity, to estimate costs for a broader societal perspective for sensitivity analysis. The SUI will also produce data on TAU for the 'index' child with ASD within each family, to ensure equivalence across trial arms and to describe ASD-related TAU within each recruitment centre. The costs of the EMPOWER-ASD intervention will be estimated from staff time (training, delivery, and supervision), facilities, and consumables collected as part of the process evaluation and cost using published national unit costs.

Health benefit for the primary analysis is the QALY (EQ-5D-5L and published utility tariffs recommended by NICE at the time of the analysis).

Regression analysis, adjusted for key covariates, will estimate the net costs and QALYs of the intervention. Missing data will be accounted for in the analyses of net costs, net QALYs and cost effectiveness acceptability. The methods used to deal with missing follow-up data will be determined according to the extent and pattern of missing data (e.g. multiple imputation, missing indicator or propensity score methods).[63,64,65] The estimates of net costs and QALYs from the regression analyses will be bootstrapped[66] to simulate 10,000 pairs of incremental cost and QALY outcomes of the EMPOWER-ASD intervention. This will include: (i) plotting the distribution of pairs of net costs and QALYs on a cost-effectiveness plane, to assess parameter uncertainty; (ii) generating a cost-effectiveness acceptability curve to estimate whether the additional cost of a QALY gained by EMPOWER-ASD is acceptable to decision makers; (iii) estimating the probability that EMPOWER-ASD is cost-effective compared to TAU; (iv) estimating a net benefit statistic.

Sensitivity analyses will explore the intervention's cost-effectiveness using: (i) GHQ-30 (parental mental health); (ii) the adapted CHU-9D (child wellbeing); (iii) wider perspective to include indirect costs of lost productivity. A simple decision model will explore the potential cost-effectiveness of the intervention over longer time horizons.

11. STUDY PROCEDURES BY VISIT

TIMEPOINT (+/- 2 months)	Enrolment/ baseline	Allocation	Follow-up (12 weeks)	Follow-up (26 weeks)	Follow-up (52 weeks)
ELIGIBILITY SCREEN	X				
REFERRAL	X				
INFORMED CONSENT	X				
ALLOCATION		X			
ADVERSE EVENTS			X	X	X
INTERVENTIONS:					
Treatment as Usual		♦—	—	—	—♦
EMPOWER-ASD Intervention		♦—	—	—	—♦
ASSESSMENTS					
Demographics & clinical information	X				
Social Communication Questionnaire	X				
General Health Questionnaire-30 (GHQ-30)	X		X	X	X
Warwick & Edinburgh Mental Wellbeing Scale (WEMWBS)	X		X	X	X
Autism Knowledge Questionnaire-UK	X		X	X	X
Reaction to Diagnosis Interview (RDI)	X		X	X	X
Reaction to Diagnosis Questionnaire (RDQ)	X		X	X	X
EuroQol Five Dimensions Health Questionnaire, 5L version (EQ-5D-5L)	X		X	X	X
Tool to measure Parenting Self Efficacy (TOPSE)	X		X	X	X
Autism Parent Stress Index	X		X	X	X
Acceptance and Action Questionnaire – II (AAQ-II)	X		X	X	X
Subthreshold Autism Questionnaire (SATQ)			X		
Autism Family Experience Questionnaire (AFEQ)	X				X
Autism Five Minute Speech Sample	X				X
Child Health Utility 9D Index (CHU-9D)	X				X
Vineland Adaptive Behaviour Scales 3 - Parent Interview	X				X
Strengths and Difficulties Questionnaire (SDQ) - Parent	X				X

Vineland Adaptive Behaviour Scales 3 - Teacher Interview	X				X
Strengths and Difficulties Questionnaire (SDQ) - Teacher	X				X
Health and Social Care Service-Use Interview (SUI)	X			X	X

12. PARTICIPANT SELECTION AND WITHDRAWAL

12.1 Participants
330 parents/primary caregivers of children aged 2-15 years with a recent ASD diagnosis recruited from 6 Greater Manchester NHS centres. All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

12.2 Inclusion criteria:
- At consent, child aged between 2 years 0 months and 15 years 11 months.
- At referral, child with a diagnosis of ASD from an NHS professional within the last 12 months. This is the age-range typically seen by ASD diagnostic teams.
- One “index” adult (child’s parent/primary caregiver; must be aged 18 years or over) per child, nominated by family on “intention to participate” basis
- Child with ASD is a patient of one of the trial collaborating centres

12.3 Exclusion criteria:
- Adult with insufficient English to preclude participation
- Adult with significant learning disability or significant hearing/visual impairment to preclude participation
- Adult with current severe psychiatric condition to preclude participation
- Significant current safeguarding concerns within family, identified by referring clinician

12.4 Setting
NHS child development centres, community paediatric services and child and adolescent mental health services in the Greater Manchester region.

12.5 Recruitment and Consent
Recruitment of participants will be via our 6 participating NHS ASD assessment teams. A local clinician will initially identify potential participating parents and screen for eligibility. The clinician will then provide a brief introduction of the trial to the parents and, with parental consent, will pass over contact details to the research team. The research team will then contact the family and have a more detailed discussion about the trial, go through the Participant Information Sheet with the parent and answer any questions they may have. Once parents have had sufficient time to consider participating, ask questions and discuss it with family and friends, the researcher will proceed with fully informed consent. Each case will be registered and assigned a participant ID number. Once 15 families have consented within a site, baseline assessment will be undertaken by Research Assistants prior to randomisation.

12.6 Randomisation

Randomisation will be conducted through the online randomisation service of the King's College London Clinical Trials Unit web-based randomisation service. Randomisation will be on an individual child basis, with one "index" parent per child, using a 2:1 ratio (10 to intervention, 5 to TAU), and stratification by recruitment centre. Supervising clinicians will contact families to feedback allocation and invite to intervention groups where applicable.

Justification for 2:1 randomisation ratio: (i) *Recruitment*: Individual parents and children will be recruited and consented at each centre as they meet eligibility criteria. Since the intervention groups are closed groups of minimum 10 (plus up to 10 accompanying adults), this means there is a potential delay in these groups forming until 15 families have consented, and the first families in each cycle will have a longer wait than those who consent and complete the set of 15 families. To mitigate against this, baseline assessments and randomisation will not be conducted until all 15 families are consented. Using 2:1 randomisation means that this process can be carried out after 15 families are consented. The use of 1:1 randomisation would require 20 families to consent before randomisation could be performed, which would lead to a longer delay for some families. This increased efficiency and reduced wait time aims to mitigate any risk of drop out between consent and treatment; (ii) *Clinical reasons*: Effective post-diagnostic support ideally takes place soon after diagnosis. Our proposed recruitment rate (please see section 5.7), a group size of 10 parents and a 2:1 ratio results in 3 intervention groups per centre/year, meaning parents will wait a maximum of 4 months between consent (which in most cases will occur soon after diagnosis) and commencement of the intervention group, which is a clinically appropriate timescale; (iii) *Design*: This is a partially nested design as there is group-level clustering in the intervention arm and no clustering in the control arm. The optimal procedure for such a design is for a greater number of participants allocated to the group intervention arm in order to account for the intra-cluster correlations in the groups - additional power is not gained here by making the two groups of equal size.[59]

12.7 Participant Withdrawal

Withdrawals can either be made by the participant or the research team. Participants may withdraw from the study at any time, without giving a reason. The research team may withdraw a participant from the study for welfare or safeguarding reasons, if their participation is no longer in their interest, or if contact for follow-up is lost for a prolonged period of time. The research team will complete a withdrawal form stating the date and reason for withdrawal. Data collected up until the point of withdrawal will be used, unless the participant has specified for their data to be destroyed. Participants will not be replaced.

13. ADVERSE EVENTS

We will collect information about adverse events at each follow-up visit and record adverse events in a standard format. Adverse Events will be monitored by the DMEC and TSC. Serious adverse events (SAEs) will be reported to the project management group and sponsor. If any of the SAEs are a suspected unexpected reaction to the intervention (it is acknowledged that this is highly unlikely in this trial), these will be reported immediately to the sponsor, research ethics committee and DMEC.

14. DATA COLLECTION AND MANAGEMENT

14.1 Data Collection
Baseline data collection will take place once 15 families have been recruited within a recruitment centre and as close to randomisation as possible. Follow-up data collection will take place at 12-, 26- and 52- weeks after randomisation. Baseline and follow-up data will be collected either via visits to participants' homes, or remotely via the use of email, postage of consent forms/questionnaires, online surveys, phones and/or videoconferencing. Researchers will sit and/or discuss over the phone/videoconference with parents during questionnaire completion to assist with understanding where necessary and to minimise missing data. Interviews will also be completed either at the parental home and/or remotely. Teacher measures will be collected by baseline and endpoint either via school/nursery visits and/or remotely, to maximise engagement and data completeness. All data collection will be carried out by the Research Associates/Assistants in accordance with trial standard operating procedures. Interviews (Reaction to Diagnosis Interview and Autism Five Minute Speech Sample) will be audio-recorded, transcribed and coded by research staff.

14.1.1 Blinding All data collection staff and their supervisors will be kept blind to group allocation; intervention practitioners and supervisors and families cannot be blinded. Parent-rated primary and secondary outcomes are not blind-rated; researcher-scored/coded secondary outcomes will be blinded (and subject to reliability checking), as will teacher-rated secondary child outcomes. Data collection staff will be uninformed on the details of the intervention. Statisticians will be kept blind. All analysis will be pre-specified and the trial dataset will be generated with a dummy variable for group allocation and the primary analysis will be conducted prior to unblinding group identities. We have established blinding procedures from our previous trials. There will be separate clinical and research leads and separate training and supervision structures. Researchers will be housed separately from staff involved in training and delivery of the EMPOWER-ASD intervention. Mid- and endpoint research assessments will be conducted so as to avoid inadvertent divulging of information that could infer treatment status. All analysis will be pre-specified and the trial dataset will be generated with a dummy variable for group allocation and the primary analysis will be conducted prior to unblinding group identities.

14.1.2 Contamination across intervention arms
To mitigate any contamination across trial arms we are recruiting only from areas which do not currently run post-diagnostic groups based on the MFT CAMHS approach. It is unlikely that families in the treatment arm of the trial will be close to other families in the control arm and unlikely that detailed intervention information would be shared between parents.

14.1.3 Fidelity
To ensure ongoing adherence to the treatment protocol 10% of randomly selected workshop sessions for each therapist will be formally coded for fidelity over the course of the study using a similar model successfully used in our previous trials.

14.2 Data Management
All trial data will be anonymised. A central paper master file of personal data will be held securely in the University of Manchester research office, to be used for operational purposes, and this will contain the key linking anonymised participant IDs to personal details. Trial data will be entered by research staff into the online database, developed and hosted by the CTU with double data checking for 100% of primary outcome, the first two cases by each individual conducting data entry and for a random 10% of cases. The trial database has a full audit trail. Appropriate quality control will be carried out during the trial and before the database lock. Primary analysis of the data will take place by the trial statisticians and Chief Investigator. Other members of the team will also have access to data and will undertake analysis as appropriate and necessary.

14.3 Data Security
Data protection and confidentiality procedures will be specified and followed, in keeping with Good Clinical Practice and the General Data Protection Regulation 2018. All audio and video recordings will be made only after written consent has been obtained from parents. Video recordings will be viewed only by members of the REACH-ASD team and for the purposes of the research and therapy, unless further explicit written consent is obtained. All video and audio recordings will be held securely in a locked cabinet, on encrypted hard-drives in accordance with pre-specified highly secure procedures. All data will be kept confidential, accessed only by the trial team. Personal information may be shared only with parental consent, e.g. with clinicians involved with the family. The only time that personal information will be shared without parental consent is if there are serious concerns about the safety or wellbeing of a child or vulnerable adult. In this event, local procedures for safeguarding children and vulnerable adults will be followed. Paper-based data collection forms will be identifiable only by participant ID and will contain no names or contact details. Personal and sensitive data will be stored separately and securely on a password-protected hard drive in a secure office. If personal information needs to be emailed, this will be in an encrypted form.

14.4 Data Retention
The data will be stored in the Faculty of Biology, Medicine and Health, University of Manchester. Paper copies will be stored centrally in secured cabinets. Electronic data will be stored within the Kings College CTU secure data storage facility and on University supported research storage systems at the University of Manchester. The custodian will be Professor Jonathan Green, Chief Investigator of the study.

At the end of the trial, the data will be stored for a period of 15 years before being destroyed.

15. STATISTICAL ANALYSIS

15.1 Sampling
Research centres will be 6 Greater Manchester NHS ASD assessment/diagnostic teams that each diagnose >120 children/year (to ensure sufficient participant pool within each centre). We will not recruit from centres that already use the Manchester workshop approach. All families meeting the inclusion/exclusion criteria will be invited into the trial and randomised in sets of 15, until the recruitment target for that

centre is reached.

15.2 Sample Size and Power

Using the Stata – clsampsi- command, we have powered on the basis of minimum clinical superiority compared to TAU. Inputs into the sample size calculations derived as conservative estimates. We account for: differential clustering because of the partial nested design, with groups of size 10, variation in group size of 10 and ICC=0.02 in treatment arm, and considering participants in TAU-only arm as clusters of size 1; baseline-endpoint correlation of 0.3 (a likely underestimate because of the repeated measures analysis); a two-sided significance level of 0.05; 2:1 allocation; an effect size of 0.4 based on effects in similar trial.[33] 90% power requires 285 participants in the analysis set: 190 participants in the treatment arm and 95 in TAU. An estimate of attrition of 15% (see below for justification) across both arms gives a recruitment total of 330 participants; 22 groups of 10 in the treatment arm. In a general adult population survey, the GHQ-30 had a standard deviation of 10.8; hence a 0.4 effect size corresponds to a 4.3 point change.[60]

15.3 Feasibility of recruitment

Excellent relationships have been built with local ASD teams through our previous and current trials: e.g. PACT (2006-09) over-recruited and PACT-G (2016-18) is recruiting to target. The context of this trial is also the integrated service development and commissioning of the Greater Manchester Health and Social Care Strategic Partnership, the executive of which is supporting this trial (see Letter of Support). Initial scoping for this application has indicated high interest, with intent to collaborate from teams that, together, make >600 diagnoses per year. We will recruit from 6 teams that each diagnose 120-200 children per year. Identifying minimum 120 new cases/centre with an estimated eligibility rate of 80% and uptake rate of 47% will recruit 45 cases/centre/year = 270 cases/year. This population is highly motivated and Hackett reports a 90% uptake to the group within her clinical service. Therefore we consider this a feasible rate. As described above, we have modelled with a 15% attrition rate; in the ASD sample within the PACT trial we had 4% attrition over a 12-month follow up.[11]

15.4 Analyses

A detailed statistical analysis plan will be approved by the Data Monitoring and Ethics Committee (DMEC) and TSC before analysis of unblinded data. Analysis will follow intention-to-treat principles and follow the CONSORT statement for non-pharmacological interventions. Analyses will post-date final follow-up assessments, with due consideration of potential biases from loss to follow-up. Baseline data will be presented using summary statistics with no testing for baseline differences.

To satisfy Objective 3, treatment effects on the primary and secondary clinical outcomes will be estimated using linear mixed models fitted to outcome variables at all time points. Fixed effects will be centre, baseline assessment for the outcome under investigation, treatment, time and time*treatment interactions. Participant and intervention group will be included as random intercepts, treating the control participants as ‘groups’ of size 1. Marginal treatment effects will be estimated for outcomes at each time point, and reported separately as mean adjusted differences in scores between the randomised groups with 95% confidence intervals and two-sided p-values. The random effect structure will account for repeated measures and

clustering due to the partial nested design, and allow estimates of the ICC in the intervention arm.

For secondary outcomes only measured at baseline and 52 weeks, the same approach will be used without the time*treatment interaction and time as fixed effects, since there is only one measurement occasion. This approach will allow for missing outcome data under the Missing At Random assumption; we may also use inverse probability weighting to adjust for non-adherence to allocated treatment and other intermediate outcomes as predictors of future loss to follow-up.

For all analyses, each intervention group will contain only the outcome measures on an index parent, and so beyond the group-level clustering, no further adjustment for multiple parents is required.

16. END OF STUDY

The end of the study will be reached when the final follow-up visit has been completed.

17. ETHICAL AND OTHER APPROVALS

Ethical approval for REACH-ASD has been sought from an NHS Ethical Committee/Health Research Authority through the Integrated Research Application System (IRAS Project ID 268914)

Any further changes or amendments to this trial protocol will be reviewed by the Health Research Authority, recorded at the beginning of the protocol.

18. TRIAL MONITORING

18.1 Sponsorship
This study is sponsored by the Manchester University NHS Foundation Trust. Monitoring and oversight arrangements appropriate to the trial's risk will be put in place.

18.2 Project Management Group
The project management group will be chaired by Chief Investigator Professor Jonathan Green and consist of the Principal Investigators, senior trial researchers and NHS practitioners, the Trial Manager, and other invited members as necessary. It will meet regularly, at least quarterly.

18.3 Trial Steering Committee
A trial steering committee (TSC) will be formed, including an independent chair, parent representatives, an NHS clinician, and an experienced triallist. The TSC will be consulted on the design, protocol, techniques for ascertainment, and measurement. The TSC will meet at least once prior to the commencement of the trial and at least annually thereafter.

18.4 Data Monitoring and Ethics Committee

There will be an independent data monitoring and ethics committee (DMEC). To be appointed.

19. DISSEMINATION AND PUBLICATION

The results of the research will be targeted for publication in peer-reviewed journals of general and special interest. There will also be a general dissemination programme for families including participants co-ordinated through our collaborators in the National Autistic Society. Individual feedback for participants will be through the regular trial newsletter.

20. FUNDING

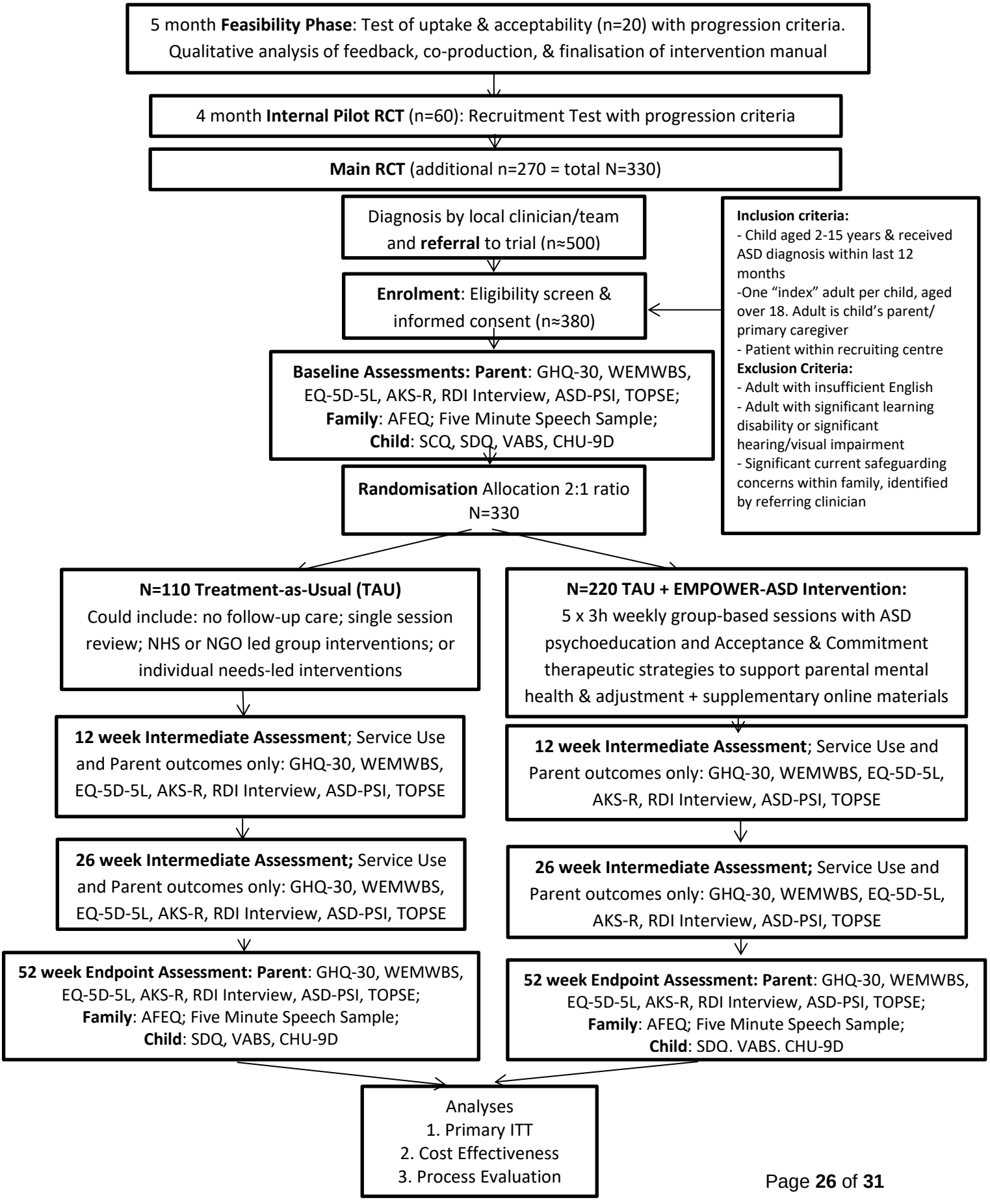
REACH-ASD is funded by the National Institute for Health Research Health Technology Assessment Board; Funder Ref: 17/80/09. Amount: £1,395,164

21. TIMELINE

Date	**Activity**
1st September 2019	Trial start
Sept-Nov 2019	Trial start-up: setting up recruitment/intervention sites; ethical and R&D approvals ; training of intervention and research staff; set-up parent advisory group; finalisation of trial protocol and SOPs; liaison with Clinical Trials Unit (CTU) & referring teams; establish TSC & DMEC; recruitment to feasibility groups.
Dec 2019 – April 2020	**Feasibility Phase:** 2x intervention groups, uptake/satisfaction data, qual feedback and analysis, co-design with advisory group/team; revision and finalisation of intervention manual, researcher practice; dev of HE measure; ongoing liaison with referrers and initial recruitment for pilot. Finalisation of AKR-S, finalisation of research procedures, randomisation system and online database.
April 2020	**Progression decision 1**
May – August 2020	**Pilot** recruitment phase: Open to recruitment 01.05.20; n=60/4 centres; First TSC meeting.
August 2020	**Progression decision 2**
Sept 2020-August 2021	**Main trial** recruitment phase; n=270/6 centres
August 2021	End of recruitment
October 2021	End of intervention
May 2021-August 2022	Follow-up phase: first endpoint 01.05.21
May – August 2022	Qualitative process evaluation data collection and analysis
Sept-Dec 2022	Data entry, cleaning and analysis

Dec 2022-Feb 2023	Dissemination through workshops to identify barriers and strategies to take the intervention to scale; modelling of costs and benefits of scaling up if found to be effective. Reporting.
End Feb 2023	Trial close

22. CONSORT DIAGRAM



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