EPICC-ID PROTOCOL

Long title of the trial	**Clinical and cost effectiveness of a parent mediated intervention to reduce challenging behaviour in pre-schoolers with moderate to severe learning disability: a randomised controlled trial**
Short title of trial	**E**valuation of **P**arent **I**ntervention for **C**hallenging Behaviour in **C**hildren with **I**ntellectual **D**isabilities (EPICC-ID)
Version and date of protocol	Version #6, 8th August 2019
Sponsor	UCL and Camden & Islington Foundation Trust
Sponsor protocol number	17/0089
Funder (s)	NIHR HTA
Trial registration number	NCT03086876
EudraCT number	N/A
Phase of trial	III
Sites	Multi-site
Chief investigator:	Professor Angela Hassiotis a.hassiotis@ucl.ac.uk
Sponsor Representative:	Suzanne Emerton uclh.randd@nhs.net

SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles of GCP the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator: Professor Angela Hassiotis

Sign:



Date: 08/08/19

Sponsor Representative:

Sign: 

Date: 04/09/2019

For the purposes of this document, PRIMENT is representing the Sponsor.

This Protocol template is intended for use with UK sites only.

VERSION HISTORY

Version number	Version date	Reason for Change
1.0	24/3/2017	Revision from submitted protocol to include further revisions requested by the funders and the CTU e.g. incl SOPs
2.0	30/06/2017	Minor inconsistency in section 11.1 regarding Expression of interest letters
3.0	25/10/2017	Extension of time period between screening and baseline, sending 'Contact' brochure and resource list to both arms of the trial, inconsistency regarding ABAS score, rebranding of 'Contact a family' as 'Contact'
4.0	18/08/2018	Addition of independent reviewer to code video-recorded parent-child interactions, the possibility of conducting qualitative interviews for the process evaluation over the phone (including verbal consent), updating the trial flowchart and clarifying the wording around the screening to baseline window and other terms and criteria.
5.0	02/10/2018	Inviting non-participating parents of ineligible children to the SSTP groups, providing further information on statistician and research assistants blinding
6.0	08/08/2019	Including the use of an external UCL approved company to transcribe qualitative interviews.Including participants in the comparison group (treatment at usual) in the qualitative interviews. Information has been added regarding the 10 month costed recruitment extension that has been approved by funders.

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2 LIST OF ABBREVIATIONS

Term	Definition
ABAS	Adaptive Behaviour Assessment System
AE	Adverse Event
ANCOVA	Analysis of covariance
APR	Annual Progress Report
CA-SUS	Child and Adolescent Service Use Schedule
CBCL	Child Behaviour Checklist
CI	Chief Investigator
CRF	Case Report Form
CSNF	Camden Special Needs Forum
CTIMP	Clinical Trial of an Investigational Medicinal Product
C-TRF	Child Behaviour Checklist Caregiver - Teacher Report Forms
DSMB	Data Safety and Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition American Psychiatric Association
EQ-5D	EuroQoL Five Dimensions Scale
EU	European Union
FOS	Revised Family Observation Schedule, FOS-RIII
GCP	Good Clinical Practice
GHQ	General Health Questionnaire
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ID	Intellectual Disability
LD	Learning Disability
Main REC	Main Research Ethics Committee
MRC	Medical Research Council
NHS R&D	National Health Service Research & Development

NIHR HTA	National Institute for Health Research Health Technology Assessment Programme
NICE	National Institute of Health and Care Excellence
Non-CTIMP	Clinical Trial without an Investigational Medicinal Product
PAG	Parent Advisory Group
PACT	Paediatric Autism Communication Trial
PedsQL	Pediatric Quality of Life
PI	Principal Investigator
PIS	Participant Information Sheet
PSOC	Parenting Sense of Competence Scale
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QRS-F	Questionnaire on Resources and Stress-short form
RA	Research Assistant
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSTP	Stepping Stones Triple P
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment as usual
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London

3 TRIAL PERSONNEL

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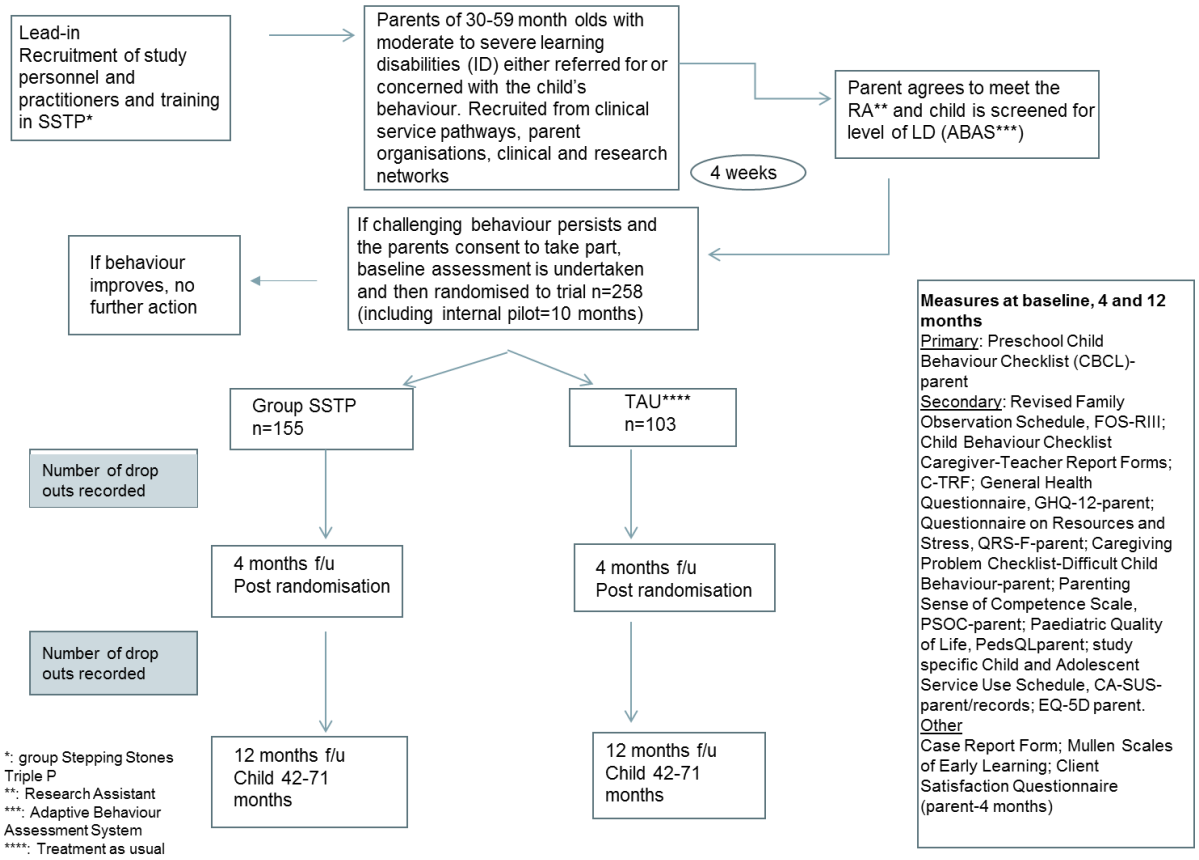
4 SUMMARY

Title:	Clinical and cost effectiveness of a parent mediated intervention to prevent challenging behaviour in pre-schoolers with moderate to severe intellectual disability: a randomised controlled trial
Short title:	**E**valuation of **P**arent **I**ntervention for **C**hallenging Behaviour in **C**hildren with **I**ntellectual **D**isabilities (EPICC-ID)
Phase of trial:	III
Objectives:	To undertake a randomised controlled trial to evaluate whether, compared to treatment as usual, level 4 Stepping Stones Triple P (SSTP) delivered over 9 weeks, reduces challenging behaviour in children with moderate to severe intellectual disability at 12 months post randomisation.
	Secondary objective

	To undertake an economic evaluation to assess the cost-effectiveness of the intervention compared to treatment as usual.
Type of trial:	Pragmatic multi-site single-blind randomised controlled trial in intellectual disabilities and challenging behaviour.
Trial duration per participant:	12 months.
Estimated total trial duration:	48 months
Planned trial sites:	4 sites (North and South London, NW England, NE England)
Total number of participants planned:	258
Main inclusion/exclusion criteria:	**Inclusion criteria** 1. Parents aged =>18 years of age 2. Child 30 to 59 months old at identification 3. Child has moderate to severe ID (screened with parent reported Adaptive Behaviour Assessment System (ABAS; General Adaptive Composite 40-69) 4. Parent report of challenging behaviour maintained over no less than 2 months **Exclusion criteria** 1. Child has profound, mild, or no ID based on ABAS 2. Parent has insufficient English language to complete study questionnaires services 3. Another sibling is enrolled in a parenting study
Methods:	Primary outcome: Parent reported severity of challenging behaviour measured by preschool Child Behaviour Check List) at 12 months post randomisation 1. Direct observations carried out by blinded research assistants (Revised Family Observation Schedule, FOS-RIII) (objective measure of parent-child interaction) 2. Caregiver reported child behaviour (Child Behaviour Checklist Caregiver-Teacher Report Forms; C-TRF) 3. Family Adjustment to Childhood Developmental Disability: A Measure of Parent Appraisal of Family Impacts 4. Satisfaction and efficacy as parent (Parenting Sense of Competence Scale, PSOC) 5. Parent psychiatric morbidity (General Health Questionnaire, GHQ) 6. Health related quality of life (Pediatric Quality of Life, PedsQL) 7. Health and social care service use (study specific Child and Adolescent Service Use Schedule, CA-SUS) 8. Parent and caregiver Health related quality of life (EQ-5D)
Statistical methodology and analysis:	A sample of 258 children is required to detect a low to moderate (standardised) effect size of 0.40 for the primary outcome CBCL at 12 months at the 5% significance level with 90% power; this is equivalent to detecting a clinically

important difference of 8 points, assuming a standard deviation of 20. The primary analysis of the CBCL score at 12 months will use mixed models to perform an individual level analysis and will follow Roberts and Roberts (2005; 2) in adjusting for therapist clustering in the intervention arm only (random coefficient model). This model will also adjust for baseline CBCL score and randomization stratification factors (centre, level of LD) using fixed effects.

5 TRIAL FLOW CHART



6 INTRODUCTION

6.1 BACKGROUND

Approximately 10% of children in the general population show challenging behaviour and it has been clearly demonstrated that when established in the preschool years such behaviours lead to worse outcomes in later life, such as criminality, lack of prospects, substance misuse and increased psychiatric morbidity (3,4,5,6).

Early intervention has been highlighted as particularly helpful and effective in bringing about change and improving longer term outcomes in children with conduct or behavioural disorders (7,8,9,10,11,12). A universal early intervention initiative was recently supported by the Prime Minister announcing parenting groups for all parents (http://www.telegraph.co.uk/news/newstopics/eureferendum/12091327/David-Cameron-plans-parenting-classes-for-all-families.html).

The Early Intervention Foundation have judged that the evidence from trials from a number of parent mediated interventions (e.g. Sure Start, VideoFeedback Sensitive Discipline, Triple P), longitudinal observational data and other health economic data, all demonstrate the importance of support as early as possible once problems have arisen (13). Further, the importance of parent mediated interventions in changing a child's behaviour is shown by evidence of the impact of social environments especially in chronically ill children. For example, parenting practices, stress and conflict as well as more generic lifestyle issues all impact on the course of childhood chronic illnesses (14).

In terms of economic gains due to early intervention, there is evidence about the return on investment in preventive programmes given that the early years are the time of maximum brain development, but also of maximum malleability (15,16,17,18). Economists have demonstrated clearly that the maximum cost benefit could be attained in the preschool years and that from school age onwards the benefit in relation to intervention cost sharply declined (17,18,19).

Intellectual disability (ID; often also called learning disability-LD- in the UK) is a lifelong condition characterized by limitations in cognitive ability and adaptive behaviours with onset during the first 18 years of life (20). Children with ID are at risk of developing challenging behaviours at a much higher rate than their typically developing peers (21,22,23,24). Moreover, longitudinal follow-up (21) showed that challenging behaviours persist over time but only 10% of participants received any intervention during the study period. A recent report by the Challenging Behaviour Foundation stated that *at all ages, children with LD are more likely to show behaviours that challenge* estimating that this applies to approximately 41,000 children aged 0-18, representing 23% of all children with ID attending schools in England (25). Of those, about 15,000 are aged 2-6 years (26), representing a sizeable proportion of children with significant morbidity who, if left untreated, are at risk of difficulties in later life. Einfeld et al (2010; 27) showed that challenging behavior increases costs of care which *affordable* early intervention programmes may be able to reverse.

We have argued that early intervention is clinically and cost effective for children in the general population and that children with ID, whilst susceptible to increased psychiatric morbidity and challenging behavior have not been afforded similar care. Whilst, there are several trials of interventions based on a range of approaches for children without ID aimed at preventing conduct disorders (8,28) there is comparatively little evidence that the presumption of preventative benefit would occur in children who have neurodevelopmental disorders and it is essential to examine this. Parent testimony supports this view:

Disabled children and their families require specific, targeted support within universal programmes; for example parents report that the universal parenting support programme can be inappropriate for parents of children with conditions that result in behaviours that challenge. The solutions for these parents and children are different from those for children without learning disabilities. Placing parents of disabled children onto universal courses can have a negative impact on parents (parent feedback to Una Summerson).

In response to the paucity of UK based research NICE, advised by the parent members of the guideline development group, recognised the importance of the problem and the need for further research (29). The guideline shows that best evidence for interventions to reduce challenging behavior in children favoured Stepping Stones Triple P (SSTP), an adapted version of Triple P (TP; 30) for children with ID. TP (and SSTP) is a system of psycho-educational and behavioural approaches to parenting a child with ID and challenging behaviour that aims to increase parental confidence and skills so that parents are able to manage the child's behavior effectively. SSTP comprises different levels based on increasing family complexity. In our study, we propose to evaluate a combination of group and individual sessions which were deemed as most appropriate for the participant group (level 4 SSTP).

Efficacy trials outside the UK have indicated significant reductions in challenging behaviour in children with ID (31). Although economic data lack for SSTP, trial and observational data from a number of countries suggest that delivery of TP may be cost-effective (32) especially if it were applied at population levels (33).

6.2 RATIONALE AND RISKS/BENEFITS

Aim

To evaluate the clinical and cost effectiveness of level 4 SSTP designed to reduce challenging behaviour in preschool children with moderate to severe ID.

Primary Hypothesis

For children with moderate to severe ID and challenging behaviour aged 30 to 59 months at the time of identification, adding level 4 SSTP to TAU will reduce challenging behaviour at 12 months post randomisation measured with the parent completed preschool Child Behaviour Checklist (CBCL) (34).

Secondary Hypotheses

For children with moderate to severe ID and challenging behaviour aged 30 to 59 months, adding level 4 SSTP to TAU will:

1. reduce challenging behaviour measured at 12 months post randomisation on caregiver completed CBCL (C-TRF)

2. reduce blind rated observed challenging behaviour in the child at 12 months post randomisation on Revised Family Observation Scales (35)

3. be cost-effective

6.3 ASSESSMENT AND MANAGEMENT OF RISK

We do not consider this trial to be high risk. Training is required but part is paid by the research funds and part by NHS excess treatment costs for therapists to be recruited to the study for one day a week for two years. Any risks are mitigated by the fact that the participating organisations will have a trained therapist who can deliver the intervention after the trial is completed. Study participants are likely to benefit by taking part in the study. However, it is possible that some parents may find groups challenging. Also, many of the questionnaires may induce some level of anxiety or worry in the parent. Therefore, it may be necessary to consider a range of steps, from offering a break, to completing the interview at a different time, to possibly raising any specific issues that arise with the clinical team. RAs will be given some guidance on how to motivate parents and we have built in individual sessions which can help with overall engagement.

All data will be anonymised and stored securely according to the UCL data protection policies.

Participants may withdraw from the study at any time but we shall clarify if data collected up to that point can be used and if not whether follow up visits are acceptable.

7 OBJECTIVES

Primary: To undertake a pragmatic randomized controlled trial to evaluate level 4 group SSTP in addition to treatment as usual (TAU).

Secondary: To undertake an economic evaluation to assess the cost-effectiveness of the intervention compared to treatment as usual

Population– children with moderate to severe intellectual disability and challenging behaviour aged 30 to 59 months at study entry

Intervention– Stepping Stones Triple P (level 4) consisting of 5 parent group sessions, followed by 3 individual sessions and one final group session as well as resource list plus guide to managing challenging behaviour by Contact.
Comparison group – Treatment as usual plus resource list plus guide to managing challenging behaviour by Contact
Outcome of interest – Parent reported challenging behaviour
Time – 12 months after randomisation with interim assessments also at 4 months after randomisation

8 OUTCOMES

8.1 PRIMARY OUTCOME

Assessment of severity of challenging behaviour at 12 months post randomisation using the parent completed preschool Child Behaviour Check List (CBC; 34). This is a robust and widely used questionnaire which measures child behavior and requires behavior to have been present for two months. It has been previously used in clinical trials and epidemiological studies of children with ID (38,39) and is extensively validated. Each question relates to a specific behaviour and is measured on a 3 point Likert Scale. Overall scores are derived for behavioural difficulties, attention problems and aggression. A T score of Total Problem Behaviours of 60/over signifies borderline to clinical caseness. CBC incorporates DSM-5 diagnostic categories which rate comorbidities, e.g. autism spectrum disorders, mood disorders.

8.2 SECONDARY OUTCOMES

1. Direct observations carried out by masked research assistants using the Revised Family Observation Schedule (FOS-RIII; 35) as an objective measure of parent-child interaction.

It has been previously used in studies investigating TP and SSTP and codes 20 minute home based videotaped parent-child interactions. The tasks to be observed include four 5-minute consecutive sections: (a) child's free play, (b) a Lego task, (c) parent and child in the same room but completing separate activities, and (d) clean-up. These tasks mimic tasks likely to happen in the home. To minimize reactivity effects, the researchers will not interact with participants and will be as unobtrusive as possible. The FOS-III codes 10 second segments and computes 4 scores: negative and positive child behavior and negative and positive parent behaviour. An independent reviewer will score all observations. There will be an inter rater reliability exercise on a proportion of the observations to ensure reliability.

2. Caregiver (not parent) reported child behaviour (Child Behaviour Checklist Caregiver-Teacher Report Forms; C-TRF). Most children in the sample age range will have additional care outside the parental home allowing us to have additional perspectives on the child's behaviour. There are positive reports about high completion rates by teachers/nursery staff as shown in other studies (40)

3. Parent psychiatric morbidity (General Health Questionnaire, GHQ; 41). This well established instrument will provide additional information about common psychiatric morbidity in the parent. It is recommended to be included in this type of studies by the Department of Health.

4. Parent stress (Questionnaire on Resources and Stress QRS-F short form; 42). Validated questionnaire which measures stress in caregivers of chronically ill or children with ID.

5. Frequency of behaviour severity during care-giving tasks (Caregiving Problem Checklist-Difficult Child Behaviour; 43). This measure assesses the frequency of difficult child behaviour when the parent is completing care-giving tasks.

6. Satisfaction and efficacy as parent (Parenting Sense of Competence Scale, PSOC; 44) The Parenting Sense of Competence scale measures parent rated competence on the dimensions of Satisfaction and Efficacy as a parent.

7. Health and social care service use (study specific Child and Adolescent Service Use Schedule, CA-SUS; 45) A modified version of the Child and Adolescent Service Use Schedule will be used in the trial. The measure is administered by a research assistant as an interview and has been developed and used in a number of evaluations of interventions in children including of preschool age e.g. PACT, TIME-A, Healthy Start Happy Start trials.

8. Health related quality of life (Pediatric Quality of Life, PedsQL; 46). The measure covers Physical, Emotional, Social, School Functioning domains. It contains a parent proxy report for children aged 2 years and over. It will be used in the study to derive QALYS for the health economic evaluation.

9. Health related quality of life in the parent/other caregiver (EQ-5D; 47). Self completed questionnaire, will capture parental and caregiver perspective on his/her health status which will be used in the economic evaluation.

Other Measures

1. Child level of disability (Mullen Scales of Early Learning; 48) (if not previously assessed) to be assessed at baseline.

2. Parent intervention acceptability (Client Satisfaction Questionnaire; 49) (to be measured at 4 months). The questionnaire will allow parents to provide feedback about the intervention by commenting on their satisfaction with and experience of the intervention, including ease of use, format and helpfulness. It has been specifically developed for research in SSTP.

3. Case Report Form (CRF) to collect sociodemographic and clinical information about comorbidities.

Schedule of assessments

Visit No	**1**	**2**	**3**	**4**
Tasks	**Screening**	**Baseline assessment***	**4 month follow up**	**12 month follow up**
Allowed deviation window	n/a	+/ week	+/- 4 weeks	+/- 4 weeks
Informed consent (screening)	x			
Assessment of eligibility criteria	x	x		
ABAS (<69)	x			
Research assessments minimum 1 week, maximum 4 weeks after screening)				
Informed consent (research)		x		
Mullen Scales of Early Learning		x		
CRF		x		

Preschool CBCL		x	x	x
Parent-child observation and FOS		x	x	x
C-TRF		x	x	x
GHQ-12		x	x	x
Questionnaire on Resources and Stress		x	x	x
Caregiving Problem Checklist-Difficult Child Behaviour		x	x	x
PSOC		x	x	x
CA-SUS		x	x	x
Client Satisfaction Questionnaire			x	
PedsQL		x	x	x
EQ-5D		x	x	x

*: at baseline, all assessments will be carried out prior to randomisation

8.3 SAMPLE SIZE AND RECRUITMENT

8.3.1 SAMPLE SIZE CALCULATION

A sample of 258 children is required to detect a low to moderate (standardised) effect size of 0.40 for the primary outcome CBCL at 12 months at the 5% significance level with 90% power; this is equivalent to detecting a clinically important difference of 8 points, assuming a standard deviation of 20. This has been calculated as follows: A standard calculation based on ANCOVA leads to a sample size of 99 children per arm, assuming a correlation of 0.5 between baseline and follow-up measurements. In order to achieve 3:2 randomisation we proceed with a calculation based on unequal randomisation (ratio=1.15) which gives group sizes of 107 and 93. Increasing the SSTP arm (only) to allow for therapist clustering leads to 139 children in the SSTP arm, assuming an intra-class correlation of 0.05 and average therapist group size of 7 (design effect = 1.3). An adjustment for anticipated drop-out of 10% leads to 155 children in the STSS group and 103 in the control group. We note that 3:2 randomisation is only slightly less efficient than the optimal 1.3:1 randomisation (5 more children are required) and is far easier to implement within blocked randomisation.

8.3.2 PLANNED RECRUITMENT RATE

We anticipate that the recruitment rates at the start of the trial are likely to be lower than recruitment rates as the trial progresses. There are an estimated 13000 children aged 2-6 years with moderate to profound ID in England with challenging behaviour although more precise estimates are unavailable (26). About 52% are likely to also have autism. Local services and the NIHR HTA funded ongoing TIME-A study data indicate that it is possible to recruit 100 children with moderate to severe ID aged 2-6 years 11 months from two children's services over 12 months and achieve 90% retention over that time. Further, studies of children with autism indicate that 8 families may need to be identified before five agree to enter a clinical trial (63% recruitment rate) (50). We estimate that we will need 22 months to recruit the total sample of 258 at a recruitment rate of 12 children per month (3 children per site per month in London, NE and NW of England). Such rates are similar to other studies of children with neurodisability (51). Data from the participating sites suggest that they receive in excess of 100 referrals a year (and as many as 300) at least a third of whom could be eligible for the study. Therefore, we are confident that we can recruit the required number of participants within our age range. We shall follow a multisource referral strategy facilitated by the clinical research networks, our national, clinical and third sector contacts and social media. If recruitment is slow, we shall open Participant Identification Centres where this is feasible and we have already lined up another potential area (Leicestershire) that would be interested in stepping in should the need arise.

A ten month recruitment extension for the study has been approved by funders. Recruitment will continue for 32 months.

9 TRIAL DESIGN

9.1 OVERALL DESIGN

Randomisation

Randomisation lists (one per site) will be prepared by the PRIMENT Clinical Trials Unit (to maintain statistician blinding) using 3:2 allocation ratio (intervention and TAU vs TAU) and will be uploaded to the external internet based randomisation and data management site Sealed Envelope prior to the study commencing. Each case will be assigned a study number and treatment allocation emailed separately to the treatment centre therapists. Eligible participants will be allocated online to the next available treatment code in the relevant randomisation list. Randomisation will be stratified by centre and level of LD (moderate and severe) and blocking will be used with random block sizes.

Blinding

As this is a study of a psychosocial intervention, the parents will be aware in which arm they have been allocated. We shall make every effort to ensure that the RAs will remain blind to arm allocation (as per study-specific guidance document) and parents will be reminded that they must not disclose any details about their treatment prior to appointments. The research assistants will be based in separate departments to those organizing and delivering the treatment ensuring masking to participant arm allocation.

To maintain statistician blinding, the study's lead statistician and the nominated Priment statistician will remain blinded as much as is feasible (e.g. trial arms will be obfuscated to group A and group B) and will maintain confidentiality concerning all aspects of the trial notwithstanding their other professional responsibilities to the safety of patients in the trial. The lead statistician will not attend the closed part of the Data Safety and Monitoring Board (DSMB) meeting.

Allocation Concealment

The RAs will enter the results of the baseline assessment on a web-based CRF. Parents and therapists will be given information about allocation status and arrangements will be made to commence the group sessions. Researchers will be housed separately from staff involved in delivery of level 4 SSTP. The therapists will not treat any family allocated to TAU.

9.2 RECRUITMENT

Study Setting

Study participants will be recruited from a wide variety of services within the participating centres in North and South London, North East (Newcastle and surrounding areas) and North West (Blackpool and surrounding areas) England. Services will include NHS settings, e.g. Child Development Teams which are the main point of referrals for children suspected with developmental delay and potentially with challenging behaviour; Child and Adolescent Mental Health Services; education (nursery/preschool) and third sector e.g. caregiver groups. Children are assessed through the Healthy Child Programme, a universal resource for 0-5 year olds which aims to identify families that require more support and children at risk of "poor outcomes".

10 SELECTION OF PARTICPANTS

10.1 Inclusion Criteria

1. Parents 18 years or over; 2. Child aged 30-59 months at identification; 3. Child has moderate to severe intellectual disability (parent reported ABAS General Adaptive Functioning 40-69; 37); 4. Written informed consent by parent/caregiver; 5. Reports of challenging behaviour over a 6- month period but no less than 2 months.

10.2 Exclusion Criteria

1. Child has mild, profound or no LD on parent reported ABAS; 2. Parent/carer has insufficient English language to complete study questionnaires; 3. Another sibling is taking part in the study

11 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

11.1 PARTICIPANT IDENTIFICATION

1. Screening: Parent rated child level of functional abilities for screening at baseline (Adaptive Behavior Assessment System-III (ABAS; 37); Parent/Primary Caregiver Form: Ages 0–5). This measure will help to decide whether a child's level of intellectual ability falls within our inclusion criteria.

The study population is parents of young children with ID concerned about their behavior living in the community in 4 different areas. We have not included children with profound ID as we deem that the intervention is not suitable to their needs and children with mild ID are also excluded as their needs are likely to be met by other available interventions. Eligible participants will be identified by the community paediatric and child and adolescent mental health teams in each of the 4 areas. Health or social care professionals will identify eligible participants through new referrals or existing cases. Identification will involve reviewing or screening identifiable personal information of participants by members of the normal clinical team. If needed, e.g. recruitment is not picking up sufficiently, we shall open Patient Identification Centres in areas adjacent to the primary sites. The professional time to be spent on participant identification has been costed through NHS support costs and a SOP will further detail the precise process at each site. All participants interested in taking part will complete an Expression of Interest form which will be then passed on to the researchers.

Flyers about the study will be put up at local parent groups, nurseries or special schools if available and GP practices.

Final eligibility for entry into the study will be confirmed by the research team who will confirm eligibility using the ABAS score.

11.2 INFORMED CONSENT PROCEDURE

The patient information sheet will be handed out by the professionals at identification of eligible participants or sent via post to identified potentially eligible participants. Parents of a child with moderate to severe ID who are worried about or have had concerns about his/her behaviour will be approached by a member of clinical staff/clinical study officer, given an introduction to the study and the study Patient Information Sheet and asked to complete an expression of interest form.

The EPICC-ID trial does not involve children that may be able to consent for themselves.

Informed consent, is two stage: First it will be obtained by the researchers from the person who has parental responsibility for the child to complete the screening measures. After a maximum of four weeks, and if the child remains eligible, the researchers will then consent the parent for the full study. Prior to any study assessments taking place, the parent will provide written or (audio-recorded) verbal informed consent. If the child is ineligible, the parent will be thanked for their time and given the reasons for this. All participants will be free to withdraw at any time from the study/intervention without giving a reason or affecting further treatment. After meeting with the RA, all parents will have at least 24 hours to decide whether to enter the study.

The researchers will be inducted in the study procedures including how to obtain informed consent and will be asked to complete the online GCP course as part of their induction.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

11.3 SCREENING PERIOD

Once a parent has expressed interest in meeting the researchers, they will need to consent to the screening process which is that the child meets inclusion/exclusion criteria. In particular, the parent administered ABAS about the child's adaptive behaviour/level of functioning and to confirm that the child has had challenging behaviours (checklist) in the past 2 months continually, i.e. such behaviours being present several times a week.

If the screening outcome is that the child's adaptive functioning does not reveal disability or mild or profound levels, then the family will be thanked for their cooperation. No further contact will be made. However, where the child fulfils the adaptive function range, the baseline assessment (assuming consent is given) will take place following which the participant will be randomised.

11.4 UNBLINDING

All cases of unblinding of researchers will be documented.

11.5 INTERNAL PILOT

The pilot will test feasibility, acceptability and recruitment at all sites, using the full baseline and eligibility and follow up assessment battery for all cases and the start-up of SSTP delivery to some of the participants. We anticipate that the recruitment rates at the start of the trial are likely to be lower than recruitment rates as the trial progresses. There are an estimated 13000 children aged 2-6 years with moderate to profound ID in England with challenging behaviour although more precise estimates are unavailable (26). About 52% are likely to also have autism. Local services and the NIHR HTA funded ongoing TIME-A study data indicate that it is possible to recruit 100 children with moderate to severe LD aged 2-6 years 11 months from two children's services over 12 months and achieve 90% retention over that time. Further, studies of children with autism indicate that 8 families may need to be identified before five agree to enter a clinical trial (63% recruitment rate) (50). We estimate that we will need 22 months to recruit the total sample of 258 at a recruitment rate of 12 children per month (3 children per site per month in London, NE and NW of England). Such rates are similar to other studies of children with neurodisability (51). We shall follow a multisource referral strategy facilitated by the clinical research networks, our national, clinical and third sector contacts and social media.

The 10 month internal pilot will allow us to assess our proposed processes, and management at all four sites in and out of London. The progression criterion is that after

initial start-up (i.e. months 5-14), the rate of recruitment at the four sites should be at least 70% of the rate expected once the trial is fully established (no fewer than 8 children per month). If recruitment rates reach this figure, it will be a clear indication that recruitment to the full study will be achievable.

During lead-in period and whilst we wait for statutory approvals, we shall formulate a recruitment strategy which incorporates principles of change and community-based participatory research practices. The former will be driven by information from the literature around what works in interventions for child mental health and will make use of the parent advisory group, our networks of parents with intellectual disabilities (e.g. coapplicants Contact) and the Challenging Behaviour Foundation. We have discussed the issues around recruitment and retention with professor Sanders, one of the SSTP developers, who has shared his experience and strategies with us.

A new study by Winslow et al (2016) describes an RCT of an engagement package which incorporates some of the ideas mentioned above and which we shall explore more systematically in our promotion of the study. Winslow et al's package includes the following components: family testimonial flyer, teacher endorsement, group leader engagement call, and brochure. The authors found that the "motivational engagement package increased parenting program initiation and attendance for parents of students at-risk for behavior problems". We shall look at which aspects are relevant to the English context, and which will be used in the present study. The therapists will have been trained by the time we are ready to begin the pilot and therefore should be able to start treatment immediately. We believe that we have taken all necessary steps to mitigate against recruitment difficulties.

Some of the methods we have described earlier will be relevant to ensuring that parents attend the treatment sessions and remain in the study. Clinical intelligence suggests that parents are able to attend the sessions on offer (similar number of sessions to SSTP) and we shall do all we can to facilitate that engagement. The treatment duration in itself is fairly brief at 6 sessions, it includes individual contact which will strengthen the relationship between parent and therapist. We shall consult with parents to negotiate the best place for the groups to run and we shall work with nurseries and GP surgeries or other appropriate community facilities (run by local authorities/third sector) in each locality to find the best fit. Further, our long term experience of studies with people with IDD suggests that very few are lost to follow up (e.g. PBS study, TIME-A study less than 10%).

We aim to offer Stepping Stones Triple P groups to parents as soon as we reach a viable group size. As the non-specific group format elements are important, if we are unable to reach a viable group size within a 3-month timeframe, we will invite other parents to attend the SSTP sessions whose children have been found ineligible to take part in the study due to the child's age or level of Intellectual Disability. These parents will be invited to attend the SSTP intervention but will not be enrolled in the study and will not complete any of the study's outcome measures.

At the end of the pilot the Trial Steering Committee will advise NIHR on proceeding to full trial if the above pre-set criteria are achieved in which case we shall continue recruiting without break.

11.6 TREATMENT PROCEDURES

Stepping Stones Triple P (SSTP) is an adaptation of the broad based parent psycho-educational intervention Triple P parenting programme adapted for children with ID. The level 4 manualised course combines six 2½ hours group sessions with three 30 minutes individual parent telephone or face to face contacts. This combination allows parents to share experiences and build on skills gained whilst including individual support. The 6 week group duration is similar to that provided by local services, e.g. parent groups run for 7

weeks. Parents receive a course book with topics to be covered in each session and if they miss a session for any reason, they will be contacted by the therapist to discuss their progress and encourage them to attend the next session. The group sessions not only educate but actively train the parents in skills and the individual consultations aim to facilitate independent problem solving. Therapists may belong to any of the professions likely to assess children with challenging behavior, e.g. psychologists, psychiatrists, social workers, family counsellors, school guidance officers, behaviour management teachers. Each therapist will run four 9 week courses per year (includes group and individual contacts) and will take part in supervision, access to the wider TP network and complete related paperwork. The learning objectives focus on maintaining behavioural change, using skills within a group learning environment, learning from peers in the group and sharing difficulties or achievements, providing support, considering if more intensive work is required, referring further if needed, talking about risk and protective factors operating within families.

A therapist is likely to spend an average of 37½ hours for each family receiving the intervention, e.g. pre-session preparation and post session reporting, fidelity checklist completion and supervision. Each therapist responsible for delivering SSTP will be trained in the Group Stepping Stones Training and Accreditation programme which includes three training days and a further half day accreditation workshop after 6 weeks. Triple P trainers will observe therapist sessions in order to build therapist competence to run the groups. Monthly supervision by VS, trained in level 4 SSTP, will also be provided in order to maintain and monitor therapist skills over time. The therapists will also have access to the Triple P providers network which provides ongoing advice about the delivery of the programme and a range of clinical resources. We aim to recruit and train eight therapists (2 per centre) to run the study groups. They will not be involved in routine care of study participants and will be based at separate facilities from the research assistants to avoid contamination and unmasking. The groups will be run in appropriate venues to be finalised closer to the commencement of the study. Issues arising from the delivery of the intervention will be raised with the designated PI and therapy coordinator at each site who will be responsible for resolving any clinical queries and maintain clinical governance.

Treatment fidelity

To determine whether treatment was delivered as intended (adherence), each therapist will complete their own session checklist and other paperwork which details what may or may not have been covered in the sessions. We shall videotape all the sessions so that they can be rated by independent assessors (competence). A random 10% of assessments will be double rated for reliability by an external blinded expert. If we assume 80% meet our fidelity criteria, we expect 95% CI 74%-85%.

Notes and video recordings may be used at supervision. Finally, we shall record therapist deviations from the manualised intervention to examine where flexibility maybe required based on individual participant needs.

Treatment As Usual (TAU)

TAU will be available to participants in both arms of the trial. It may include a range of services such as:

1. Health visitor services; 2. Primary care engagement and advice; 3. Potentially some version of early intervention maybe provided by either community paediatric services or Child and Adolescent Mental Health Services, although our understanding is that very little is available for children of this age. 4. Parenting advice and support sessions by carers groups or other third sector organisations.

Parents allocated to both arms of the trial will receive a list of national resources and the Contact guide to challenging behavior with tips and advice on social and health care supports.

Prior to the commencing contact with potential participants we shall collect information about the type and extent of services available to the parents of young children with neurodisability at all study sites.

11.7 PROCESS EVALUATION

The process evaluation, overseen by KO and JB, will be based on the revised MRC recommendations (36). Understanding how psychosocial interventions work in practice is an essential element of future uptake within services, therefore, it will inform all aspects of the trial. There has not been previous information about the delivery of SSTP within the UK NHS context. The process evaluation will begin during the pilot phase as some of the groups will begin and complete during the initial 10 months of the study. We shall utilise a mixed methods approach including assessment of what is delivered (fidelity, dose, adaptations, reach), collection of the opinions of a stratified purposive stakeholder sample, i.e. participants (those who have been allocated to treatment as usual, those taken part in the intervention as well as those who have declined approximately 10-12 from each); 6-8 service managers; and therapists (all). We may need to revise those numbers depending on whether saturation is reached.

Participants will be approached at around 4 months which would be coterminous with the 1st follow up visit. For participants who decline to take part, we shall endeavour to ask at initial approach whether they would be willing to be interviewed about their reasons for non-participation as there would be implications for future SSTP implementation. We shall explore current policy guidance as it becomes available and we shall formulate hypotheses as to the facilitators and barriers to the delivery of level 4 SSTP.

Interviews for the process evaluation will be conducted either face-to-face in the family home or another convenient place, or over the telephone. Interviews will be audio-recorded and transcribed verbatim. Transcriptions of qualitative interviews will be conducted by a UCL-approved specialised and reputable company external to UCL. Approximately 15 interviews will be transcribed using this service.

We will obtain either verbal or written consent for the interviews conducted as part of the process evaluation prior to conducting the interview. For written consent, we will follow the same consent procedures as per protocol. When obtaining verbal consent we shall send the relevant information sheet in advance and shall then contact the person by telephone in order to gain their consent to participate. The verbal consent process will be audio recorded and the recordings will be securely stored.

As part of the process evaluation parents will be asked for their views of the intervention. Parents will be given a brief SSTP intervention survey at the end of the final group session.

11.8 DEFINITION OF END OF TRIAL

The end of the trial will be the date of the last visit/ telephone follow up/ home visit by the last participant. We have specified a window of -/+ 4 weeks around that date.

11.9 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND 'STOPPING RULES'

Participants may drop out of the intervention sessions or may also drop out of the project. It is our experience that participants may still wish to meet with the researchers but not take part in interventions. Therefore, although we shall stress that participants can withdraw at any time without giving a reason, we shall retain any assessment records that have been

carried out to that point and we shall maintain contact unless told otherwise. All contacts with participants and reasons for withdrawing or dropping out completely will be documented.

11.10 CONCOMITANT MEDICATION

This is a trial of a psychosocial intervention. As far as we are aware many of the children taking part are unlikely to be receiving psychotropic medication through they may receive other drugs for co-existing medical conditions. We shall record all medications taken by the children as part of the CRF and resource use procedures.

11.11 POST-TRIAL ARRANGEMENTS

There are no arrangements made for the intervention to be made available to the trial participants after the trial is completed.

12 DATA MANAGEMENT

All aspects of data management of the study will comply with the UK Data Protection Act 1998, PRIMENT SOPs and Good Clinical Practice. We shall be using the Data Safe Haven as managed and monitored by UCL personnel and in discussion with the NHS sites taking part in the study. The Data Safe Haven is a secure system for storing sensitive information. Once data such as audio and video recordings are uploaded into it, will be erased from the digital machines with which they were originally recorded. The system will be set up for the study and will be supported by the UCL Data Safe Haven Support Officers.

12.1 CONFIDENTIALITY

The Case Report Forms (CRFs) will not bear the participant's name. The participant's initials, date of birth and trial identification number will be used for identification. Any personal data collected will be managed according to PRIMENT SOP Managing Personal Data.

12.2 DATA COLLECTION TOOLS

The data collection tools will be created according to PRIMENT SOP Development, Review and Approval of Case Report Forms.

12.3 TRIAL DATABASE

The CRFs will be entered into a web-based clinical data management system, Red Pill, provided by Sealed Envelope through PRIMENT. Sealed Envelope has been assessed by PRIMENT to ensure that adequate processes are in place and are being followed for quality management, software development and security. Database services and support will be delivered through a contract signed by Sealed Envelope and UCL.

PRIMENT SOPs Validating Sealed Envelope Systems and Change Control for Sealed Envelope Systems will be followed to set up and manage changes to the trial database.

At the end of the trial, prior to analysis, PRIMENT SOP Database Lock, Unlock and Closure will be followed.

12.4 DATA COLLECTION AND HANDLING

All data will be collected and handled in accordance with PRIMENT SOP Data Handling.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

12.5 DATA OWNERSHIP

At the end of the trial, the data belongs to UCL.

13 RECORD KEEPING AND ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of study report. We shall follow the Sponsor guidance on archiving and digitising EPICC-ID records and related materials (http://www.ucl.ac.uk/library/research-support/research-data/best-practices/guides/storing).

Chief Investigators are responsible for the secure archiving of essential trial documents (for each site, if multi-site trial) and the trial database as per their trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the Sponsor.

14 STATISTICAL CONSIDERATIONS

Dr Gareth Ambler is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

14.1 STATISTICAL ANALYSES

14.1.1 PRIMARY OUTCOME ANALYSIS

The analyses and subsequent reporting will be guided by the Consort recommendations (http://www.consort-statement.org/). We shall construct a Consort diagram to describe the flow of subjects through the study and we shall summarise the characteristics of the children in each study arm and compare these visually to assess whether balance has been achieved. Any notable imbalances may lead to additional adjusted analyses. The primary analysis of the CBCL score at 12 months will use mixed models to perform an individual level analysis and will follow Roberts and Roberts (2005; 2) in adjusting for therapist clustering in the intervention arm only (random coefficient model). This model will also adjust for baseline CBCL score and randomization stratification factors (centre, level of ID) using fixed effects. All modelling assumptions will be checked and a confirmatory analysis will be performed using the heteroscedastic model (52). Additional analyses will be performed for each of the secondary outcomes. Continuous outcomes will be analysed in a similar manner to that described for the primary outcome but for binary outcomes we shall use logistic mixed models (52). Missing data will be explored. Specifically, we shall quantify the amount of missing data in each trial arm and investigate the impact on the balance achieved by randomisation. We shall also explore whether missingness is associated with any participant characteristics and may require further adjusted analyses to be carried out. We have made no adjustment for multiple testing as we are interested in the effectiveness of SSTP at both time points.

14.1.2 SECONDARY OUTCOME ANALYSIS

Description of the approach planned to analyse secondary outcomes. Secondary outcome analyses should be considered as hypothesis generating rather than providing firm conclusions.

14.1.3 SENSITIVITY AND OTHER PLANNED ANALYSES

A description of plans for sensitivity and other analyses. For example sensitivity to missing data or non-compliance.

Please note that a more detailed statistical analysis plan should be produced as a separate document at some point prior to the final analysis (as recommended by the ICHE9 guidelines). In this document, a more technical and detailed elaboration of the principal features stated in the protocol should be included. The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the blind review of the data and should be finalized before breaking the blind. Formal records should be kept of when the statistical analysis plan was finalized as well as when the blind was subsequently broken.

14.2 INTERIM ANALYSIS

None planned

14.3 OTHER STATISTICAL CONSIDERATIONS

The study will be overseen by a Data Safety and Monitoring Board (DSMB) which includes an independent statistician. We shall respond to any queries raised and Dr Ambler will be attending the meetings as required. The DSMB we shall also have annual meetings to manage the trial procedures. The final analysis plan will be devised and discussed at a later stage once all the data are in and prior to cleaning and database locking. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

15 QUALITATIVE METHODS

We shall use topic guides developed with input from the parent advisory group and the interviews will be audio-recorded and transcribed with full anonymisation. We shall set up the analytical framework to enable us to organise the data. Transcriptions will be conducted by a UCL-approved' specialised and reputable company external to UCL. The preferred method is a framework approach to the thematic analysis of the transcripts (63). Although sensitive to the stakeholders' views the overall approach will be primarily deductive based on previous literature and the specifics of our study. A collaborative process of analysis will involve several members of the research team who will read transcripts and discuss emerging coding ideas which will help to enhance analysis validity.

16 ECONOMIC EVALUATION

The primary analysis for the economic evaluation will be conducted from the health and social care (HSC) perspective with a secondary analysis from the societal perspective that will include the impact on quality of life and productivity of parents and other caregivers contributing to the child's care.

Information on parent resource utilisation will be obtained using the CA-SUS. We will ask about health and social care resource use utilization in the past 6 months at baseline and 12 month follow-up and in the past 4 months at 4 month follow-up. The primary analysis will include only data health and social care data collected as part of the trial and hence cover only 10 months of the trial (missing months 4 to 6). We will project costs from 4 month and 12 month follow-up to estimate the 12 month health and social care resource use as part of sensitivity analyses. UK unit costs obtained from publicly available sources will be applied to each resource item in both arms of the trial (53,54). Benefits payments will be costed from government statistics. Data on delivery of the intervention will be collected to calculate the

cost of the intervention using micro-costing methods (55).The overall economic evaluation will comprise:

1. Cost-effectiveness analysis: mean incremental cost from the HSC perspective per change in CBCL. Incremental cost-effectiveness ratios will be reported and uncertainty explored using cost-effectiveness acceptability curves (56,57). 2. Exploratory analysis of quality of life using PedsQL to predict utility scores: the use of Health-Related Quality of Life instruments in children is increasingly adopted in clinical trials and permits standardised measurement and comparison between studies (56). There is no single, valid, preference-based measure for health state valuation in children under the age of 5 or children with LD and therefore it is not currently possible to calculate a QALY for use in cost-utility analysis (58). PedsQL showed feasibility, reliability and validity in children with learning and developmental disabilities (59). As a result, we shall use the PedsQL General Score Scale and the mapped EQ-5D-Y utility scores algorithm (60,61) to calculate QALYs. 3. Cost-benefit analysis of impact on the parents and other caregivers: Responses to EQ-5D will be used to calculate QALYs in a standard format and valued as a willingness to pay for a QALY gained. Information on productivity losses will be collected and costed using the human capital approach (62). As caring responsibilities of caregivers are complementary to state funded caring we shall also calculate the societal value of caring provided by family and other caregivers.

Confidence intervals for costs and QALYs will be generated using bootstrapping. We will include adjustment for baseline values (costs, CBCL and utilities) in the 3 analyses above. Missing data and adjustment for other covariates will mirror the statistical analysis plan.

17 NAME OF COMMITTEES INVOLVED IN TRIAL

The trial will be overseen by the TSC and DSMB which will comprise of at least 75% independent members. The remit will be according to the HTA guidelines. Meetings will be annually but maybe more, e.g. twice a year as needed. At least 50% of the meetings will be face to face.

The Trial Management Group (TMG) (*all trials should have a TMG*), Data Safety and Monitoring Board (DSMB) and Trial Review Group (TRG). The terms of reference and/ or charters for these committees will need to be provided in separate documents.

If there is not to be a DSMB, state why.

18 RECORDING AND REPORTING OF ADVERSE EVENTS AND REACTIONS

18.1 DEFINITIONS

Term	Definition
Serious Adverse Event (SAE)	Any untoward occurrence that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect • is otherwise considered medically significant by the investigator

Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is deemed to be • Related to the trial intervention AND • Unexpected (not listed in the protocol as an expected side effect of the intervention)

18.2 EXPECTED SIDE EFFECTS

As with any research involving questionnaires which ask about personal matters, it is possible that some parents may experience distress or discomfort and be reminded of their child's disability. Parents may also be upset due to their existing relationships with services and professionals and some of those perceptions may influence their views about interventions and potential for benefit/harm.

18.3 RECORDING ADVERSE EVENTS

AEs/SAEs will be collected by the trial manager who will be seeking that information from the PIs and reported via the eCRF within 24 hours of becoming aware of the event. All reports of SAEs will be reviewed by the CI or PIs within 2 days of receiving the report and the review outcome will be recorded in the eCRF .

18.4 ASSESMENTS OF ADVERSE EVENTS

Each serious adverse event will be assessed to determine if the event is related to the intervention and if the event is expected.

A. RELATED EVENTS

The assessment of the relationship between adverse events and the administration of the intervention is a decision based on all available information at the time of the completion of the case report form. If the event is a result of the administration of any of the research procedures then it will be classed as related.

B. EXPECTED EVENTS

If the event has been listed in the protocol (section 18.2) as an expected side effect of the intervention then the event will be classed as expected. If the event is not listed then it will be classed as unexpected.

18.5 PROCEDURES FOR REPORTING SERIOUS ADVERSE EVENTS

Any serious adverse events which are classed as related and unexpected will be reported to the ethics committee that approved the trial and to Priment. The reporting of adverse events to the ethics committee and sponsor will be completed according to Priment non-CTIMP safety management SOP.
SAEs will be reported by the CI (delegated to the Trial Manager). The Chief Investigator (or their delegate) is responsible for reporting SUSARs to the ethics committee that approved the study within 15 calendar days of becoming aware of the event.

18.6 THE TYPE AND DURATION OF THE FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

SAEs will be followed up until resolved. If the investigators become aware of safety information that appears to be related to the treatment, involving a participant even after the individual has completed the study, this will be reported to the sponsor.

18.7 ANNUAL PROGRESS REPORTS

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The Chief Investigator will prepare the APR.

18.8 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken, the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to REC of the measures taken and the circumstances giving rise to those measures.

18.9 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

A “serious breach” is a breach which is likely to affect to a significant degree –

(a) The safety or physical or mental integrity of the participants of the trial; or

(b) The scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor’s SOP on ‘serious breaches’ will be followed.

19 MONITORING AND DURATION

A monitoring plan will be established for the trial based on the risk assessment. The trial will be monitored with the agreed plan.

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

The overall project duration is 58 months. We shall allow five months lead-in prior to study commencing. We shall obtain all required permissions; develop protocol and other documentation (e.g. CRF); register the study, begin to publicise it, advertise for, recruit and appoint to the posts of trial manager, research assistants and therapists. Book therapists into SSTP training course.

Funded set up phase

Months 1-4: Develop and launch trial website; therapist training and monitoring of competence; induct research assistants into study procedures (e.g. training and reliability work, set up of and training in data entry and record systems, site closure procedures), induct local investigators; begin recruitment activities in multiple sites. TMG and PAG meeting

Internal pilot

Months 5-14: Begin recruiting and randomization of participants into the study; monitor its progress; site visits; set up groups and begin delivery of SSTP at all sites. Aim to confirm recruitment strategies work and that we can retain participants during this time. Begin work on process evaluation; TSC and DSMB meetings; TMG and PAG meetings; report to TSC about carrying on with recruitment and treatment if criteria are met; Funder agreement to continue funding. Protocol publication; conference attendance

On going recruitment and follow up

Months 15-50: Continue with recruitment (up to month 38 over a 32 month period) and follow up of participants (month 50 last follow up), continue process evaluation. Continue with TMG and PAG meetings. TSC and DSMB meetings. Conference attendance

Final phase

Month 51-58: Site closures; completion of process evaluation; data cleaning and analysis; draft report; dissemination.

20 REGULATORY REQUIREMENTS

In order to carry out the study, we will apply for HRA approval which includes independent ethical review and assessment of regulatory compliance. At each study centre, we shall publicise the study widely among colleagues in Child Development Centres, Child and Adolescent Mental Health services, local nurseries and third sector organisations, e.g. facilitating parent groups. This process will be oversee by co-applicants in the participating areas (MT, AS, MK, JT). Members of the research team will present the study at local academic and lay/open meetings.

20.1 PUBLIC AND PATIENT INVOLVEMENT

The views of parents of children with LD and challenging behaviour from the Camden Special Needs Forum (CSNF) helped us to develop this proposal and they have told us that they would like to continue to be involved. We have had verbal feedback from the group leaders Samantha Akita and Linnet McIntyre about how helpful and interesting the parents have found the meetings. US also carried a consultation with parents; one said: *if I had been involved with this trial when my son was younger I'm sure I would be in a very different place today. If we had the right strategies to use earlier, I could have gone back to work and the school wouldn't be ringing me all the time-no more illegal exclusions…*

We held two face to face meetings with CSNF parents from a diverse ethnic background on 13th January 2016 (for the outline) and 19th April 2016 for the main application. We have also had extensive email correspondence and discussions with the CSNF group leaders and with our co-applicants Contact regarding the best way to involve the parents. We have agreed on the following plan:

We shall recruit four parents who will form the study Parent Advisory Group (PAG) which will be facilitated by co-applicant MK. We shall provide PAG with a one day seminar regarding the research and their role in it prior to starting. They will be involved in overseeing the trial, discussing study progress, helping with materials, e.g. information sheets and consent forms, advertising the study, input to the topic guides, carrying out speaking and workshop engagements, other dissemination and attending the Trial Management Group. The PAG will be asked to comment on a draft of the full study report and will also help us to determine the content of the summary outlining the study findings to be disseminated to the study participants if they wish to receive them.

21 FINANCE

The study is funded by the NIHR HTA (15/162/02).

22 INSURANCE

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in an NHS organisation or an organisation contracted to the NHS an NHS organisation or an organisation contracted to the NHS continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the NHS organisation or an organisation contracted to the NHS's duty of care, or any negligence on the part of NHS organisation employees. This applies whether the NHS organisation is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

NHS organisation selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

23 PUBLICATION POLICY

Our dissemination/communication plan has several strands:
1. We shall develop and launch a project website which will publish information about the study and host the protocol, study materials, newsletters, presentations and publications relating to it. We shall utilise social media such as facebook and twitter to reach parents, services and commissioners and other stakeholders to further our dissemination and maintain interest in the study.
2. We shall produce newsletters which will be sent to all participants and participating services every six months with study updates
3. We shall publish the study papers in high impact journals and shall make available through our institutional portals (Green) as well as also publishing some in Open Access journals (Gold).
5. We will publish targeted communications for parents through Contact which will also host a link to the study website. They will also advise on other media and policy opportunities that allow us to disseminate our findings.

6. We will communicate our findings at local, national and international conferences including those that address lay and parent groups
7. We shall hold a one day conference once the findings are known with invitees from parent and policy organisations, NHS England, clinicians and commissioners of services.
8. We shall produce a study report for the funders which will be posted on the HTA website
9. We shall work with the UCL Policy Unit to prepare briefings of the findings for policy makers and other stakeholders.

Parents will be involved at stages and take part in commenting on reports and papers prior to publication as well as leading on presentations.

24 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

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