A PRAGMATIC RANDOMISED CONTROLLED TRIAL OF SENSORY INTEGRATION THERAPY VERSUS USUAL CARE FOR SENSORY PROCESSING DIFFICULTIES IN AUTISM SPECTRUM DISORDER IN CHILDREN: IMPACT ON BEHAVIOURAL DIFFICULTIES, ADAPTIVE SKILLS AND SOCIALISATION

(SENITA)

PROTOCOL VERSION 3.0, 04.05.2017

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National Institute for Health Research

SIGNATURE PAGE

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 outlined in the relevant trial regulations, GCP guidelines, and Sponsor's SOPs.

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

Director:		
Name	**Signature**	**Date**
Chief Investigator:		
Name	**Signature**	**Date**
Co-chief Investigator:		
Name	**Signature**	**Date**

General Information This protocol describes the SenITA clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR

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Trial Co-ordination:

The SenITA trial is being coordinated by South East Wales Trials Unit, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit which is part of the Cardiff University Centre for Trials Research (CTR).

This protocol has been developed by the SenITA Trial Management Group (TMG).

For **all queries** please contact the SenITA team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

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Randomisations:

Randomisation
Randomisation will be completed by the research team only.
(See section 9.5 for more details).

Clinical queries:

Clinical queries
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All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the Study Team within 24 hours of becoming aware of the event (See section 13 for more details).
Contact details: SenITA@Cardiff.ac.uk
SAE number: 02920 687608

Table of Contents

Glossary of abbreviations

ABC	Aberrant Behaviour Checklist
ADOS	Autism Diagnostic Observation Schedule
AE	Adverse Event
APSI	Autism Parenting Stress Index
ASD	Autism Spectrum Disorder
CAMHS	Child and Adolescent Mental Health Services
CarerQOL	Carer Quality of Life
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DMEC	Data Monitoring Ethics Committee
EQ5D	EuroQol five dimensions questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HB	Health Board
HE	Health Economics
HTA	Health Technology Assessment
ICH	International Conference on Harmonization
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIAG	Participant Information Advisory Group
PIS	Participant Information Sheet
PSS	Personal Social Services
QA	Quality Assurance
QALY	Quality-adjusted Life Years
QC	Quality control
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
SAE	Serious Adverse Event
SIPT	Sensory Integration and Praxis Test
SIT	Sensory Integration Therapy
SOP	Standard Operating Procedure
SP	Sensory Processing
SPM	Sensory Processing Measure
SSI	Site Specific Information
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Usual Care

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

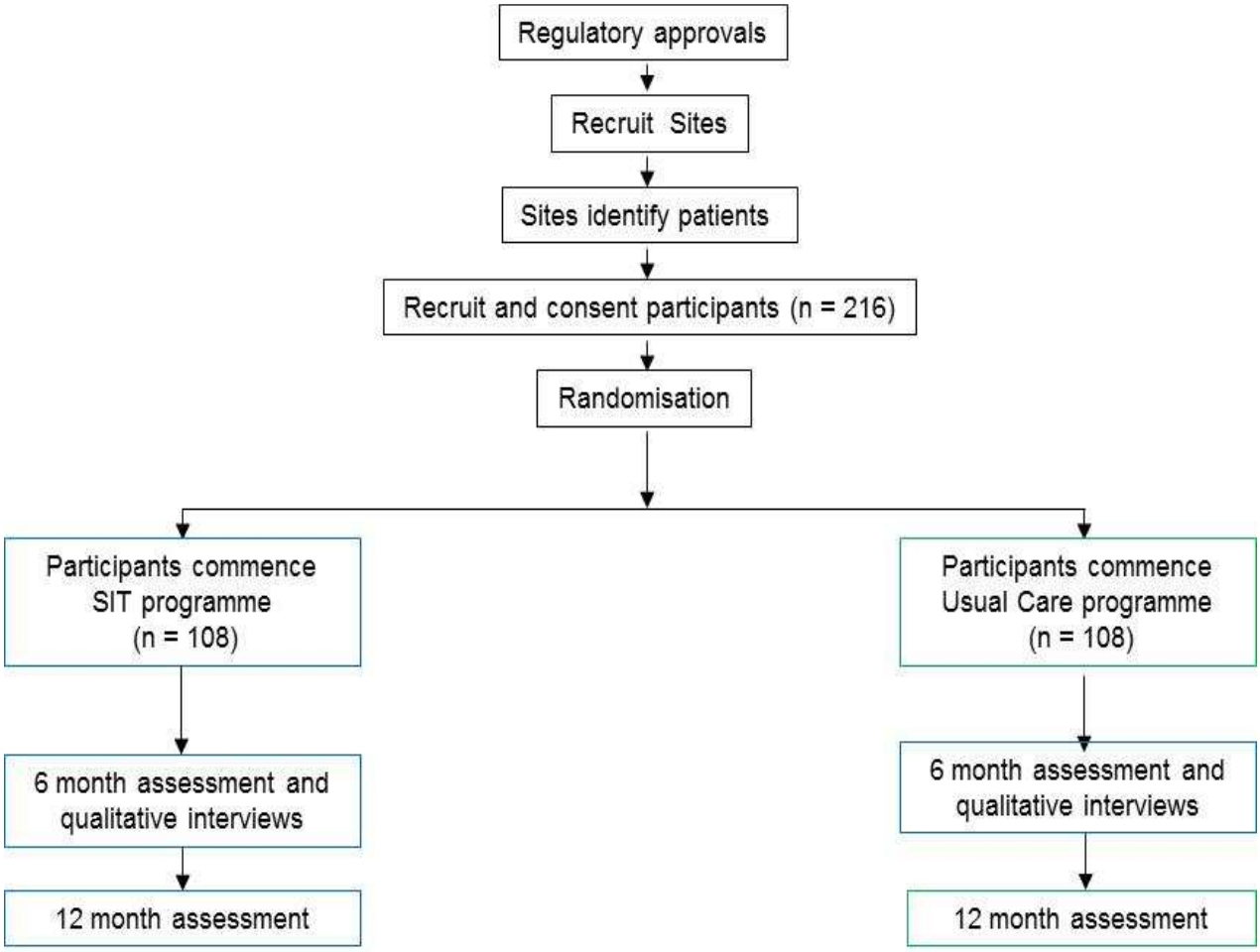
Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
3. Substantial (submitted to REC as SA1)	3.0	04.05.2017	1. Safeguarding process has been defined in relation to reporting and/or escalating any concerns arising from the final phone call intervention sessions.

2 Synopsis

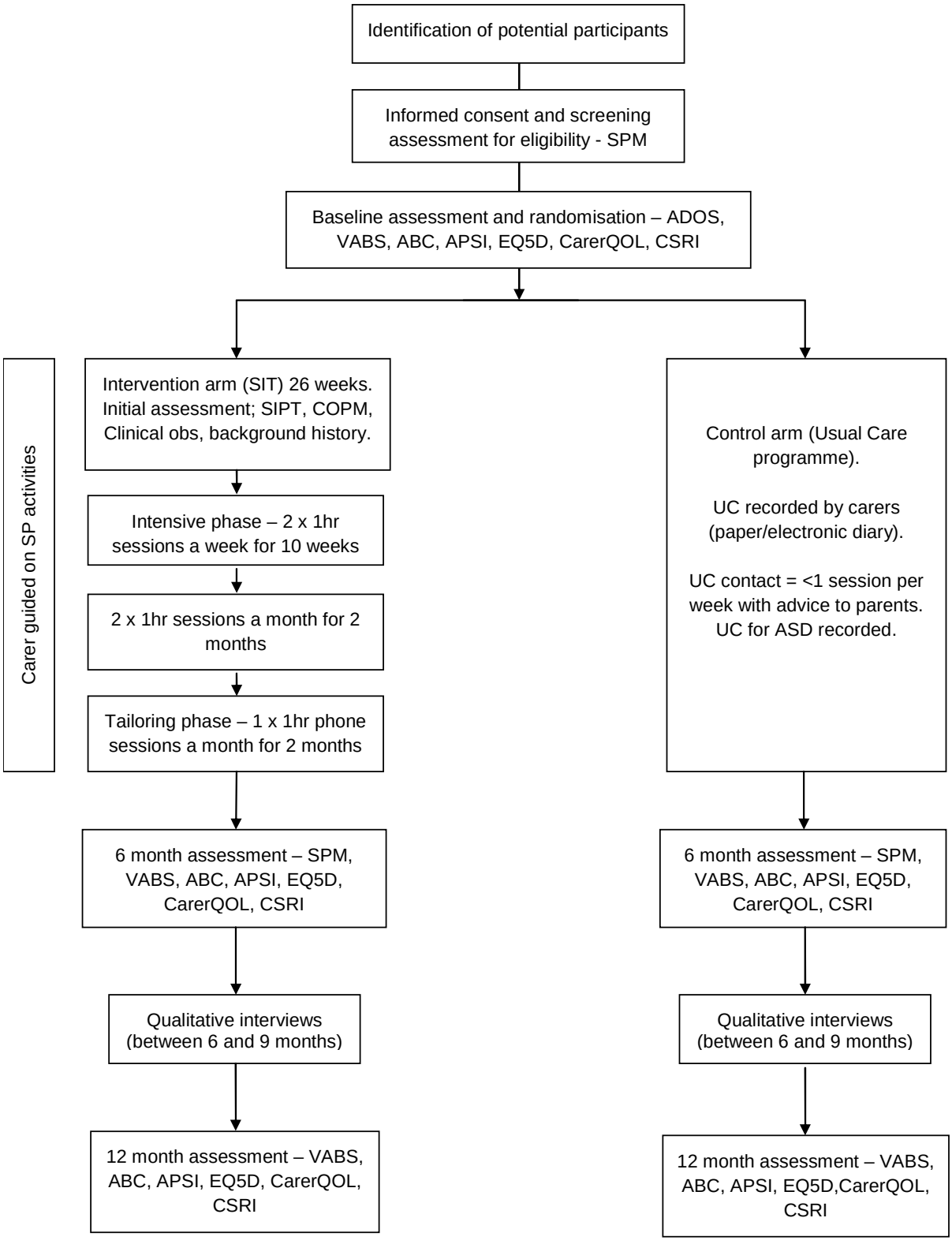
Short title	Sensory integration therapy versus usual care for sensory processing difficulties in ASD in children.
Acronym	SenITA
Internal ref. no.	SPON1568-16
Clinical phase	n/a
Funder and ref.	NIHR Health Technology Assessment programme (HTA)
Trial design	Two-arm pragmatic individually Randomised Controlled Trial (RCT)
Trial participants	Children between the ages of 4 and 11 with ASD and sensory processing difficulties.
Planned sample size	216 children
Inclusion criteria	ASD; in mainstream primary education for the duration of the trial (4-11 yrs); definite/probable SP difficulties (SPM); carer consent/child assent.
Exclusion criteria	Current/previous SIT; current Applied Behaviour Analysis therapy.
Treatment duration	26 weeks
Follow-up duration	12 months
Planned trial period	39 months
Primary objective	To determine the impact of SIT on irritability and agitation, as measured by the corresponding sub-scale of the Aberrant Behaviour Checklist (ABC).
Secondary objectives	(i) effectiveness of SIT for additional behavioural difficulties or challenging behaviour such as hyperactivity/non-compliance, lethargy/social withdrawal, stereotypic behaviour, inappropriate speech (ii) the impact of SIT on adaptive skills, functioning and socialisation (iii) sensory processing scores post-intervention (i.e. at six months) as a potential mediator of any association observed between SIT and the primary outcome at 12 months (iv) age, severity of SP difficulties, adaptive behaviour, socialisation and comorbid conditions as potential moderators of any association between SIT and irritability/agitation, adaptive functioning (child) and carer stress (v) the impact of the intervention on carer stress and Quality of Life (QoL) (vi) cost-effectiveness of the intervention, including direct intervention costs, health, social care, education services, carer expenses and lost productivity costs (vii) fidelity, recruitment, acceptability, adherence, adverse effects and contamination in a process evaluation conducted alongside the main trial.
Primary outcomes	Irritability/agitation at 6 months (ABC-I)
Secondary outcomes	Other problem behaviour (ABC subscales); adaptive behaviours, socialisation and functional change (VABS-II); carer stress (APSI) and QoL (EQ5D; CarerQol)
Intervention	SIT (Ayres Sensory Integration®) in 26 1-hr sessions (2 per week for 10 weeks, 2 per month for 2 months, 1 telephone session per month for 2 months. A sample will be fidelity-assessed.)

3 Trial summary & schema

3.1 Trial schema



3.2 Participant flow diagram



3.3 Trial lay summary

Autism Spectrum Disorder (ASD) is a common lifelong condition affecting 1 in 100 people. ASD affects how a person relates to others and the world around them. Difficulty responding to sensory information (noise, touch, movement, taste, sight) is common in ASD. This might include feeling overwhelmed or distressed by loud or constant low-level noise e.g. in the classroom. Affected children may also show little or no response to these sensory cues. These 'sensory processing difficulties' are associated with behaviour and socialisation problems, and affect education, relationships, and participation in daily life. Sensory Integration Therapy (SIT) is a type of face-to-face therapy or treatment, provided by trained occupational therapists. The therapist uses play -based sensory-motor activities to influence the way the child responds to sensation, reducing distress and improving concentration and interaction with others.

Research suggests SIT might be helpful for some children. In this study we are interested in whether, compared to treatment normally offered to families ('usual care'), SIT improves the child's behaviour socialisation and daily functioning. Usual care could involve some contact with an occupational therapist, who might give parents or carers strategies to practice at home with their child. It is much less common though to be offered the kind of structured one-to-one regular contact involved in SIT (24 face-to-face sessions, 2 telephone sessions over 26 weeks in this study). We will compare SIT to usual care in a sample of 216 children and will assess behaviour, daily functioning, socialisation, and parent/carer stress at 6 and 12 months using questionnaires. Those who agree to take part will be allocated at random to either SIT or usual care by an online programme. Discussion groups for therapists and carers will be organised before approaching people to take part, so that what people normally receive as 'usual care' can be mapped out. Carers will be given diaries (paper-based or electronic) to record their contact with NHS and other services (e.g. social care).

A sample of carers will be interviewed at 6 months to gain their views and experiences of taking part in the study and of their child's sensory problems. Therapists will also be interviewed in order to get a sense of what intervention was actually provided to people in the study. The cost of providing this type of treatment, compared to usual care will be assessed. Once approximately 10% of study participants have completed the 6-month assessment, a sample of carer diaries will be examined to see whether SIT is different (in content or amount of contact) to usual care. The study will only continue if this is confirmed. The study team will also look at the number of people willing to take part and whether they continue to participate in all sessions and assessments.

At the end of the trial, an event for affected families will be organised to publicise the results. A summary will also be made available to organisations like NAS to include on their websites and for dissemination via social media.

4 Background and rationale

Difficulties in processing sensory information are common in ASD with prevalence estimates of 90-95%[1-3]. Such difficulties result in hyper or hypo-reactivity to sensory input and may occur due to impaired regulation of central nervous system arousal[4]. This hyper-reactivity may result in challenging behaviour such as aggression (due to poor tolerance of noise/touch), or additional "safe space" needs in the home[5]. Impaired sensory processing may also result in poor motor control impacting on participation in daily life. There is substantial potential burden associated with sensory processing difficulties for children with ASD, their carers and families, and also to the NHS in terms of treating consequences such as challenging behaviour or behavioural difficulties. Sensory processing difficulties also pose significant challenges in mainstream educational settings. The potential pathway of effect is unconfirmed but it is plausible that reducing sensory processing difficulties could lead to improvements across behavioural, social and educational dimensions.

A variety of potential therapies have been proposed, but there needs to be a clear distinction between Sensory-Based Interventions (SBIs) and Sensory Integration Therapy (SIT). SBIs are usually sensory strategies applied to the child or made available to the child for regulation of their reactivity within the home or school environment. Adaptations to family routines and environment may be suggested. Current research into the effectiveness of these SBIs is insufficient to recommend their use, especially if they are not individualised to the child[6]. However, this is currently the most common form of 'usual care'. SIT is a clinic-based approach that focuses on the therapist-child relationship and uses play-based sensory motor activities designed to address sensory-motor factors specific to the child to improve their ability to process and integrate sensation[7]. SIT shows some promise as a potential therapy[8-10] but research is limited and in some cases interventions evaluated do not meet fidelity criteria for SIT or are poorly defined[6]. Although Sensory Integration Therapy is currently offered by the NHS in some regions, in their recent guidance document[11] the National Institute for Health and Care Excellence (NICE) reported that available evidence was of low quality and therefore insufficient to recommend treatment.

The key aims of the trial proposed in this application are to: (i) describe current usual care in trial regions and clearly differentiate this from the proposed intervention (Sensory Integration Therapy); (ii) to evaluate the clinical effectiveness of SIT in a two-arm pragmatic RCT as a therapy for sensory processing difficulties in young children with ASD. The intervention will be evaluated in terms of impact on behavioural problems and adaptive skills, socialisation, carer stress, quality of life and

cost-effectiveness. Participants with a range of ASD and sensory symptom severity, as well as functional and cognitive ability will be recruited from NHS, educational and third sector settings. The primary outcome time-point is post intervention (six months), reassessed at 12 months to determine whether any observed effects are maintained in the longer-term. An internal pilot will examine whether the intervention differs significantly in content or intensity from usual care, and assess recruitment and retention. Contamination, adherence and fidelity of intervention delivery will be measured as part of the process evaluation conducted alongside the trial.

We believe this research will benefit the NHS in terms of providing clear evidence regarding the effectiveness and cost-effectiveness of this type of intervention thereby informing clinical practice for this population. We also strongly believe that children and their families will benefit from receiving treatment informed by a more robust evidence base, whether or not SIT itself is effective. Furthermore, if SIT is effective, the proposed intervention could significantly improve behavioural, functional, social, educational and well-being outcomes for children and well-being outcomes for carers and families. Subgroup analyses will also help to determine which children and families would be most likely to benefit, thereby maximising cost-effective roll-out.

5 Trial objectives and outcome measures

The key aim is to answer the following research question: 'What is the clinical and cost-effectiveness of sensory integration therapy for children with autism spectrum disorder?' We propose to examine, in a two-arm pragmatic individually Randomised Controlled Trial (RCT), the effectiveness of manualised Ayres Sensory Integration® therapy (SIT) for children with Autism Spectrum Disorder (ASD) and Sensory Processing (SP) difficulties. Throughout this document, use of the word 'carer' will refer to parents or individuals with parental responsibilities.

5.1 Primary objectives

The primary objective is to determine the impact of SIT on irritability and agitation, as measured by the corresponding sub-scale of the Aberrant Behaviour Checklist (ABC).

5.2 Secondary objectives

Secondary objectives are to evaluate:

i. effectiveness of SIT for additional behavioural difficulties or challenging behaviour such as hyperactivity/non-compliance, lethargy/social withdrawal, stereotypic behaviour, inappropriate speech
ii. the impact of SIT on adaptive skills, functioning and socialisation
iii. sensory processing scores post-intervention (i.e. at six months) as a potential mediator of any association observed between SIT and the primary outcome at 12 months
iv. age, severity of SP difficulties, adaptive behaviour, socialisation and comorbid conditions as potential moderators of any association between SIT and irritability/agitation, adaptive functioning (child) and carer stress
v. the impact of the intervention on carer stress and Quality of Life (QoL)
vi. cost-effectiveness of the intervention, including direct intervention costs, health, social care, education services, carer expenses and lost productivity costs
vii. fidelity, recruitment, acceptability, adherence, adverse effects and contamination in a process evaluation conducted alongside the main trial. An internal pilot with specific progression criteria will assess the feasibility of proposed recruitment and trial retention rates. Pre-recruitment, a brief survey of OTs and a series of focus groups/interviews with therapists and carers will inform the definition of Usual Care (UC), which at most is likely to comprise sensory-based input or intervention not meeting fidelity criteria for full SIT, or awaiting specific services. The trial will only progress should a qualitative assessment of carer-held diaries conclude that the intervention arm is sufficiently different from usual care. During the pilot phase (complete once at least 11 participants in the SIT arm and 11 in the UC arm have completed the post-intervention/six-month follow-up assessment) estimates of the mean and pooled SD of the ABC-I at the primary outcome time-point, and the proportion of participants providing primary outcome data will also be obtained. Demonstration of adequate fidelity of intervention delivery (scoring 80 or above on the fidelity measure[12] across 80% of sessions sampled) will be measured as part of the process evaluation. As an 'effective' dose for SIT is yet to be established, adherence to the intervention is not a progression criterion. However, attending 13 of a possible 20 sessions delivered during the

intensive intervention phase (two thirds) is likely to indicate sufficient exposure based on clinical experience.

5.3 Primary outcomes measure

The primary outcome, to be measured at baseline, six and 12 months is irritability/agitation as measured by the corresponding Aberrant Behaviour Checklist sub-scale (Community version ABC-I: 15 items[13, 14]). The primary outcome time point is at six months (i.e. post-intervention) in the SIT arm. The primary outcome comparison is based on carer ratings of ABC-I. However, teacher/teaching assistant ratings of ABC-I (assessed at six month follow-up only in both arms) will be explored in terms of the potential impact of carer response bias.

5.4 Secondary outcomes measures

Problem behaviours: Other problem behaviours will be measured at baseline, six and 12 months using the remaining four ABC sub-scales: lethargy/social withdrawal (16 items), stereotypic behaviour (seven items), hyperactivity/non-compliance (16 items), and inappropriate speech (four items). Although moderate correlations between sub-scales are generally observed, researchers are advised not to use a total score as construct validity is poor[13, 15, 16]. For all ABC sub-scales, items are rated on four-point Likert scales (ranging from 0=not at all a problem to 3=the problem is severe in degree).

Adaptive behaviours, socialisation and functional change: Adaptive behaviours, socialisation and functional change will be assessed at baseline, six and 12 months using the Vineland Adaptive Behaviour Scales (VABS-II: parent/carer rating version[17]). VABS-II comprises four main domains: communication (receptive, expressive, written); daily living skills (personal, domestic, community); socialisation (interpersonal relationships, play and leisure time, coping skills) and motor skills (gross and fine motor skills).

Carer stress: Carer stress will be assessed using the Autism Parenting Stress Index (APSI[18]) at baseline, six and 12 months. The APSI is a 13-item measure of parental stress covering the social, physical and behavioural issues that characterise ASD. Each item is scored according to four categories: ‘not at all stressful’; ‘sometimes creates stress’; ‘often creates stress’; so stressful that sometimes I/we feel we cannot cope’.

Quality of Life: Carer quality of life will be measured using two measures the EQ5D 5L[19] scale and CarerQol[20]. EQ5D is a health-related Quality of Life (QoL) scale comprising the following five dimensions assed via single items with a three-category response option: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ5D is recommended for use in health technology assessments, and also includes a measure of general self-related health on a vertical visual analogue scale with endpoints labelled 'best imaginable health state' and 'worst imaginable health state'. The Care-related Quality of Life instrument (CarerQol) will be used to measure and value the impact of providing informal care on carers. It combines a subjective burden measure that provides a comprehensive description of the caregiving situation using the CarerQol-7D with a valuation of informal care in terms of well-being (CarerQol-VAS)[20]. The CarerQol has been shown to be valid in populations of caregivers of children with ASD[21].

Mediators

Scores on the SPM[22] are also assessed at six months (in addition to screening) in order to determine whether any effects of the intervention on the primary outcome at 12 months (if observed) are mediated by severity of SP difficulty post-intervention.

Cost-effectiveness outcomes

Detailed information on staff and non-staff inputs directly associated with the SIT intervention and UC will be recorded for each participant during the intervention period. Data on services and support external to the interventions will be collected at interview for each participant in the study at baseline (covering the previous 6 months), at six and 12 months. The Client Service Receipt Inventory[23] will be adapted for use in this study on the basis of expert opinion and used to collect service and support data covering: inpatient stays, outpatient and day-patient attendances, accident and emergency attendances, contact with school and community-based professionals such as, education welfare officer, counsellor (school or community), speech and language therapist (school or community), physiotherapist, psychologist (educational or clinical), community paediatrician, child and adolescent psychiatrist, general practitioner, nurse (either school or practice), social worker, nutritionist/dietician, therapist (art or music or drama or play). Costs will be calculated for each service by multiplying each service type (e.g. accident and emergency attendances, contact with school or community-based professional) by an appropriate unit cost. The Client Service Receipt Inventory will be adapted to not only collect service and support data for the child but will also collect health and social care services used by the child's main carer including carer out-of-pocket

expenses and time taken off work because of their child's Autism Spectrum Disorder and sensory processing difficulties.

Productivity losses will be calculated by multiplying reported time taken off work by the paid carer's wage rate. The main cost-effectiveness analyses will be conducted from a NHS and PSS perspective. Secondary analyses will adopt a societal perspective, adding education services, carer out-of-pocket expenses and lost productivity to NHS and PSS. The ABC-I at six-months will be used, in turn, as measures of effectiveness in a series of cost-effectiveness analyses. The main cost-effectiveness measure is incremental cost per point improvement in ABC-I (6m).

5.5 Screening and baselines measures

Screening measure

The Sensory Processing Measure (SPM Home Form[22]) is included at screening to confirm definite/probable sensory processing difficulties. This version of the measure provides eight standard scores for the following dimensions: social participation; vision; hearing; touch; body awareness (proprioception); balance and motion (vestibular function); planning and ideas (praxis) and a total sensory symptoms score. Scores on each of these dimensions are classified as either: typical; some problems or definite dysfunction. For the purposes of the current trial, sensory processing difficulty is defined as either: (a) a definite dysfunction on at least one sensory dimension (defined as all domains except social participation) and the total score or (b) a probable dysfunction on at least two sensory dimensions and the total score. Treating therapists will access these scores in order to aid with delivery of the intervention.

Baseline only measure

In order to characterise the recruited sample according to ASD symptoms, the Autism Diagnostic Observation Schedule[24] (ADOS) will be included as a baseline measure. The ADOS is not being used as a diagnostic tool to determine eligibility for the study (the inclusion criteria relate to an existing relevant clinical diagnosis).

6 Trial design and setting

The trial is a two arm individually randomised effectiveness trial comparing manualised Sensory Integration Therapy (SIT) to Usual Care (UC) for primary school aged children with Autism Spectrum Disorder (ASD) and Sensory Processing (SP) difficulties. The target is to recruit 216 children between the ages of 4 and 11 years from multiple sources: Child and Adolescent Mental Health Services (CAMHS), occupational therapy services, paediatric clinics, primary schools, support and or social services and via self-referral. Therapy will be delivered in clinics meeting full fidelity criteria (structural equipment elements) for manualised SIT.

Those in the intervention arm will receive SIT in 26 1-hr sessions (Face-to-face: 2 per week for 10 weeks, 2 per month for 2 months; Phone call: 1 per month for 2 months) with a sample fidelity-assessed[12]. The comparator arm is usual care (UC) which is defined as awaiting services or sensory based intervention not meeting SIT fidelity criteria (e.g. 1 face-to-face session per week or less). An online survey, focus groups and interviews will map the provision of UC.

An internal pilot with progression criteria will assess: recruitment, retention and whether UC differs from expected provision. A process evaluation will examine contamination, fidelity of intervention delivery, adherence and any adverse effects. Therapist and carer interviews will explore: barriers/facilitators, adherence, therapeutic relationship, mechanisms of change, SP deficit, engagement in activities and contamination. Interview and focus group data will be double-coded and analysed using thematic analysis[25].

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment includes:

- The known and potential risks and benefits to human participants
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as low risk, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section on monitoring).

7 Site and Investigator selection

Secondary care NHS and private occupational therapy treatment settings (where NHS capacity is insufficient to support the current trial/no appropriate NHS treatment settings are available) across South Wales and in South West England will be included as research sites, provided they meet the structural fidelity criteria for intervention delivery.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place:

- The approval letter from the site's R&D Department, following submission of the Site Specific Information (SSI) form
- A signed Trial Agreement
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheets and Consent Forms.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator detailing that the centre is now ready to recruit participants into the trial. This confirmation must be filed in each site's Site File. Along with the written confirmation, the site should receive a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It

is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

8.1 Inclusion criteria

Participants must:

i. have a diagnosis of ASD (as documented on medical and/or educational records), OR have probable/likely ASD (defined as currently being assessed within the local ASD pathway);
ii. remain in mainstream primary education for the duration of the trial (age range 4-11 yrs);
iii. have definite or probable SP difficulties defined as (a) a definite dysfunction on at least one sensory dimension (defined as all domains except social participation) and the total score on the Sensory Processing Measure (SPM)[22] or (b) a probable dysfunction on at least two sensory dimensions and the total score;
iv. provide carer consent/child assent.

8.2 Exclusion criteria

Other than the obverse of the inclusion criteria, participants will be excluded if:

i. Currently undergoing or previously undergone SIT
ii. Currently undergoing Applied Behavior Analysis therapy.

9 Recruitment, Screening and registration

9.1 Informing carers of potentially eligible children about the trial

Participants will be recruited from CAMHS/paediatrics, occupational therapy, schools and support/social services. Where possible, carers of children who have been referred to these services will be sent a letter by that service informing them about the trial, and a participant information sheet (PIS), along with advice on how to get in touch with the study team. The study will also be advertised on relevant websites (i.e. related charities' websites) and via social media and trial specific website. It will also be possible for carers to make a self-referral.

9.2 Screening logs

A screening log of all ineligible and eligible but not consented/not approached will be kept at each site so that any biases from differential recruitment will be detected. When at site, logs may contain identifiable information but this **must** be redacted prior to being sent to the CTU. The screening log should be sent to the SenITA email account every month (see section 21 for further detail on data monitoring/quality assurance).

9.3 Recruitment rates

There are approximately 119,868 children aged four to 11 years within the areas covered by Cardiff and Vale University, Cwm Taf and Aneurin Bevan Health Boards[26]. Assuming approximately 1% of these children have ASD[27, 28] of whom 90% are likely to experience sensory processing difficulties[1, 2], 70% of whom are educated in mainstream schools[29], then the eligible population will be approximately 755 across the three Health Boards and we will aim to recruit approximately 75% of our sample (n=162) from this population. Approximately 25% of participants (n=54) will be recruited from within Cornwall Partnership NHS Foundation Trust (from an eligible population of approximately 270[29, 30]. Therefore approximately 20-25% of the likely eligible population will be recruited across both regions. We have modelled recruitment and intervention delivery using the most likely scenarios and estimate approximately seven SI therapists will be required, each delivering the intervention to a total of 15 intervention arm participants over a period of 21 months

(total recruitment rate is approximately seven participants per month during the first three months and approximately 11 per month thereafter).

9.4 Informed consent

Potential participants will have a range of impairments and some are likely to have a degree of intellectual disability. No child will be excluded on this basis, or due to other co-morbid conditions, provided all other inclusion criteria are met and exclusion criteria not met. Informed consent from carers and assent from children will be sought by suitably qualified, experienced and trained personnel in accordance with the GCP directive on taking consent and before any trial related procedures are undertaken.

Written informed consent will be obtained from the child's carer (their parent or legal guardian). The participant and their carer will be given sufficient time after the initial invitation to participate before being asked to sign the consent form. Carers will also be consenting to their participation in the trial (which includes completion of some outcome measures), also for the study team to contact the child's school. The school maybe be asked for feedback on the child's behaviour and will also be asked to complete the ABC-I at 6 months. Carers will be notified that they can withdraw consent for their and their child's participation in the trial at any time during the trial period. For all children, the person taking consent will assess the child's capacity to understand the nature of the trial. An age appropriate information sheet will be supplied where appropriate and the views of children capable of expressing an opinion will be taken into account. Children who are deemed to have capacity and are able to write, will be asked to sign an age appropriate assent form.

Video recording: Assessment of fidelity and supervision require sessions to be video recorded. Clear distinction will be made between consenting to use of recorded sessions specifically for assessing fidelity of treatment and supervision of therapist in this trial and for consent for use in future research or training opportunities. The latter will be detailed on a separate form to the main trial consent form. Denying consent to be video recorded does not affect the participants' eligibility to take part in the trial. One copy of the consent form will be given to the participant, the original copy will remain with the investigator for the site file and a further copy should be kept with participant's clinical notes.

After the participant has entered the trial, the therapist must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

Separate informed consent will also be taken for participation in the qualitative interviews.

We will comply with Welsh language requirements and the PIS, Consent Form and any other required participant documentation will be available in Welsh. However, all documentation used for data collection (i.e. outcome measures) will remain in English as they are designed and validated in English.

9.5 Randomisation

Following screening, consent and collection of baseline data, participants will be randomly allocated to usual care or SIT in a 1:1 ratio. Online randomisation will utilise minimisation with a random component used to allocate participants to the group that causes the least imbalance. Allocations will be minimised by site, severity of sensory processing difficulty, and sex of the child.

10 Withdrawal & loss to follow-up

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal of Trial Treatment/ Intervention
2. Withdrawal from questionnaires
3. Withdrawal from follow-up assessments
4. Withdrawal of Consent to all of the above

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. Unless otherwise specified, participant data already collected prior to withdrawal will be retained according to the trial protocol..

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly: If a participant wishes to stop taking part in the trial completely, they may need to be seen one last time for an assessment.

A participant may withdraw or be withdrawn from trial intervention for the following reasons:

- Withdrawal of consent for treatment by the participant
- Any alteration in the participants condition which justifies the discontinuation of the intervention in the Investigator's opinion
- Non-compliance

In all instances where a participant consents and subsequently withdraws, a withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal form should be sent to the trial team. Any queries relating to potential withdrawal of a participant should be forwarded to the trial manager.

We will make every effort to reduce loss to follow-up using the methods listed below:

1. We will emphasise the importance of getting follow-up data at baseline and follow-up.
2. We will send birthday cards to participants and newsletters and with a 'change of address' form to those in both trial arms.
3. We will arrange to complete follow-ups in the carer' homes or somewhere convenient to them so they won't have to travel far.
4. We will send two reminders to ask carers to return the postal questionnaire and will rearrange follow-ups twice for those who do not attend an arranged appointment.
5. We will obtain carers mobile phone numbers so we can contact them directly to arrange follow-up.
6. We will complete over the telephone the key questionnaires for non-responders so we have a minimum data set.
7. Carers will be offered £10 in high street vouchers at each follow-up assessment time point.

11 Trial Intervention

11.1 Sensory Integration Therapy

Those allocated to the intervention arm will receive 26 one-hour sessions of SIT (Ayres Sensory Integration®[31, 32]), delivered over 26 weeks: two sessions per week for 10 weeks (intensive phase), followed by two sessions per month for two months, then one telephone session per month for two months (tailoring phase). A detailed assessment (SIT arm only) of sensory processing deficit will be undertaken (Sensory Integration and Praxis Tests: SIPT[33]) along with clinical observations post-randomisation. Following this assessment, the data will be analysed and a hypothesis developed as to the nature of the underlying sensory difficulty affecting function. In addition, background history, and the Canadian Occupational Performance Measure (COPM)[34] will be carried out. This allows the sensory-motor content of the SI therapy (proprioceptive, vestibular or tactile) to be individualised to meet the specific needs and functional goals of the participant. SIT uses the 'just right' challenge for each child and is therefore able to adjust the therapy to functional ability (as measured at baseline). Carers will be encouraged to observe or actively participate in sessions to facilitate engagement. Between sessions carers will be given brief written guidelines of specific sensory-motor activities to support their child's sensory integration. Success of these strategies will be discussed at the following session.

The intervention will be delivered by occupational therapists (typically NHS Band 7) trained in SIT meeting fidelity criteria in regional clinics. Initially clinics will be located in Cardiff, Newport and Caerphilly in South Wales and Cornwall with the potential for more to be included based on recruitment rates and therapist availability. In some instances, the therapist may be joined by a student in the session – present to support the carer if required – who will not be delivering the intervention. Intervention therapists will be supervised/mentored prior to and during the trial by an SI trained therapist. Therapists will be given feedback on the first two video recorded sessions they deliver, which will be assessed for fidelity as described below. Supervision/mentoring sessions of approximately one hour in length will be provided fortnightly during the first two months of the intervention delivery phase, tapering to once per month or at least once every 6 weeks thereafter. A Facebook group will also be set-up for treating therapists to join should they wish. This will be a forum for them to support each other in the trial. Intervention therapists will provide therapy to

participants recruited to the SIT arm only. Those participants receiving any form of usual care (such as provision of sensory strategies and/or face-to-face sessions delivered once per week or less) will be seen by occupational therapists not delivering SIT in the current trial.

11.2 Fidelity assessment

Fidelity of intervention delivery will be assessed using the Ayres Sensory Integration® Intervention Fidelity Measure[12]. Structural fidelity is assessed according to level of therapist training/qualifications, followed by a score of 85/110 for four areas: safety of the environment, detail and content of therapist-held records including therapist-carer collaboration in relation to goals set during therapy, physical space and equipment, and communication with carers. In addition, the intervention sessions will be measured for process fidelity to determine whether the therapist: ensures physical safety; provides sensory opportunities; helps the child to maintain appropriate level of alertness; challenges postural, ocular, oral or bilateral motor control; challenges praxis and behavioural organisation; collaborates in activity choice; tailors activity to provide appropriate challenge; ensures activities are successful; supports intrinsic motivation to play; establishes therapeutic alliance. The scale demonstrates high content validity according to expert ratings and high reliability for process elements (total score ICC 0.99; Crohnbach's α 0.99)[12].

Where consent is provided, face-to-face sessions will be video-recorded. Fidelity of delivery will be assessed through the first two video recorded face-face sessions delivered to any participant for each therapist to ensure any training required to achieve acceptable fidelity is provided (re-assessed if indicated) at the earliest opportunity. A sample of recorded sessions in the intensive phase will also be rated for fidelity by an independent SIT-trained therapist (based on a randomly selected minimum 15-20 minute sample of the full sessions). Demonstration of adequate fidelity of intervention delivery is defined as scoring 85 or above on the fidelity measure[12] across at least 80% of sessions sampled.

If we can identify suitable additional resources at a later date, we also use the video recording to look into fidelity of delivery in more detail. As part of this, we will include specific items to gauge the impact of non-specific therapist effects, using an adapted version of a tool developed for evaluation of psychosocial interventions for individuals with intellectual disability [35, 36]. The tool includes specific items to assess: session structure (agenda setting; maintains clear focus; avoids straying

from the remit of the intervention; asks for feedback from previous and current session); communication (conveys understanding by checking, rephrasing or summarising; shows sensitivity by adjusting content/style of communication to help client/carer understanding; communicates clearly without frequent hesitation; maintains a good pace of communication and activity) and alliance (shows empathy; shows warmth and respect for client).

11.3 Comparator

Usual Care (UC) will be recorded by carers in diary format (paper-based/electronic according to preference). The current standard care pathway is variable across the UK, ranging from minimal contact/no specific treatment targeted at sensory processing, to provision of manualised SIT in some regions. However, within the proposed trial sites, we estimate that usual care will be much less intensive than the 26-week intervention programme detailed above, ranging from some provision of sensory strategies not meeting full fidelity criteria for SIT (and should not occur more frequently than once per week) to no specific treatment. Within Aneurin Bevan Health Board for example, usual care consists of an initial screening assessment for functional difficulties, followed if required by a range of services depending on the clinicians' experience and reasoning. This may involve a limited number of one-to-one sessions with the child (e.g. six), but more often is in terms of advice to carers on sensory strategies and environmental adaptations with intermittent follow up. Notes will be kept according to usual policy. Therapist experience may be variable but their fidelity of treatment delivery will be measured as part of the process evaluation. Usual care for ASD will also be recorded more generally including any contact with NHS services (e.g. speech therapy, paediatrics and CAMHS).

Usual care for the current trial will be assessed and fully defined following a brief pre-recruitment survey of therapists, and discussions (e.g. as interviews or focus groups) with carers and occupational therapists. The potential for contamination, if participants recruited to the UC arm receive enhanced/additional support from clinicians who are aware of their participation in the trial is acknowledged thus there will be an examination as to whether the UC received differs in any way from the expected provision mapped out as a result of the scoping focus groups.

12 Trial procedures

12.1 Internal pilot and progression criteria for full trial

An initial internal pilot phase will assess feasibility of recruitment, retention to the intervention and the nature of UC for sensory processing difficulties in the control arm. It is expected that UC will comprise use of sensory-based strategies not meeting fidelity criteria for the SIT intervention, and of no treatment at all in a significant proportion of cases.

Progression criteria are as follows:

1. Recruitment feasibility criteria will be met if at least 70% of those approached meet eligibility criteria for trial entry and at least 50% of those eligible are willing to be randomised. We estimate an average recruitment rate of seven per month for the first three months (study months 4-6), and 11 per month for the remaining pilot period (months 6-12) equating to 87 participants in total across both arms in a nine month period (months 4-12). Overall recruitment rates will be formally reviewed at this time point, and should the trial team and Trial Steering Committee be in agreement that recruitment rates are significantly below those predicted with no obvious mitigating or modifiable factors (such as differing site opening dates across regions), recruitment will not continue past this point. Participants already recruited however would receive the intervention and be followed up as planned.
2. Once 11 participants in the SIT arm and 11 in the UC arm have completed the post-intervention/six-month follow-up (approximately 10% of the total sample), carer-completed diaries will be qualitatively assessed to determine whether UC is sufficiently different from the SIT intervention for the full trial to continue. Broadly defined, this criterion will be met provided those in the UC arm do not receive any intervention meeting criteria for full SIT. Within Aneurin Bevan Health Board UC consists of an initial screening assessment for functional difficulties, and if required this is followed by a range of services depending on the clinician's experience and reasoning. It may involve a limited number of one-to-one sessions with the child but more often is in terms of advice to carers on sensory strategies and environmental adaptations with intermittent follow up. UC for this study however will be assessed and fully described following the brief therapist survey and pre-recruitment focus groups with carers and occupational therapists.

3. If dropout at the first follow-up time point exceeds 20% the sample size calculation and associated implications for feasibility of recruitment will re-assess.
4. To confirm the accuracy of the sample size calculation and other features of the proposed design, an estimate of the following will be obtained: (a) proportion of participants providing primary outcome data; (b) SD of the ABC-I at the primary outcome time point (post-intervention) in both SIT and UC groups; (c) intra-cluster correlation coefficient (ICC) of SIT therapists within participants for the ABC-I at the primary outcome time point (post-intervention, SIT arm only).

Although not progression criteria, fidelity of intervention delivery and adherence will be measured as part of the ongoing process evaluation. By the end of the internal pilot phase, a random sample of SIT sessions (at least 15 – 20 minutes of the session) delivered by all therapists will have been evaluated using the fidelity measure with video footage to establish acceptable fidelity of intervention delivery. In order to demonstrate adequate fidelity, it is expected that therapists will score 85/110 on the process fidelity measure[12] for at least 80% of sessions rated. An 'effective' dose for SIT has not yet been established. However, based on clinical experience and currently available evidence [6, 8-10] attending 13 of a possible 20 sessions delivered during the intensive intervention phase (two thirds) is likely to indicate sufficient exposure.

12.2 Staff training

All staff involved in trial specific procedures (including recruitment/consent, collection of trial data, delivery intervention) will be trained in the required elements of good clinical practice (GCP). Training materials will be designed for training of trial site staff, including the PI and any other designated staff involved in the trial.

Therapists will be given full training in how to identify potential participants and all aspects of their involvement in the trial. Once a patient has consented to take part in this trial, the therapist will ensure that this is made clear on the patients' medical notes should any other clinician see the patient at any other time.

12.3 SIT sessions

Participants in the intervention arm will receive SIT delivered in 26 one hour sessions. At first this will be as two sessions per week for 10 weeks in the intensive phase. It will then taper to two sessions per month for two months and then one telephone session per month for two months. Where the intervention is delivered as a telephone session, the therapist will ensure that safeguarding procedures for reporting and / or escalating any concerns arising from these sessions (as detailed in the Intervention handbook) are adhered to.

It will be the participating therapist's responsibility to provide participants with details of each of these appointments at the first visit, record them on an appointment card which is to be given to the participant or their carer and to remind them of the appointment nearer the time of the visit to ensure attendance. The therapist will also be responsible for re-arranging any appointments as necessary. In the event that a participant cannot attend a session, there will be up to two attempts made to reschedule keeping within +/- 3 days of the original appointment. Any that cannot be rearranged will be foregone.

The appointment card will also contain the therapists contact details and an emergency number for participants or carers to use should they need it. It is important that the therapist is the first point of contact should there be any concern.

As part of each session, the therapist will maintain documentation of the intervention delivery. They will also confirm the participant and their carer are happy for the session to be video recorded. At the end of the session the therapist will upload the video recording of the session to secure servers at the CTR for fidelity analysis. Once transferred, they will be deleted from the therapist's recording device.

12.4 Assessments

Details of outcomes and follow up time points can be seen in Table 1 and are the same for both experimental and control groups. Assessments will be performed as close as possible to the required time point.

Table 1. Schedule of enrolment, interventions and assessments

Procedures	Visits

	Screening	Baseline	Treatment Phase	Follow Up	
				6 Months	12 Months
Informed consent	X				
Demographics					
Eligibility assessment - Sensory Processing Measure (SPM)	X			X	
Randomisation		X			
ABC		X		X	X
ABC-I (teacher rated)				X	
ADOS		X			
APSI		X		X	X
CarerQOL		X		X	X
CSRI		X		X	X
EQ5D		X		X	X
VABS		X		X	X
Delivery of intervention (including initial assessment)			X		
Diary completion			X		
SAEs		←as required→			
Withdrawals		←as required→			

In the event that participants' follow up appointments are missed at the proposed time points, the research team will contact the carer by telephone to rearrange the appointment as soon as possible. In the event that telephone contact is not successful, then reminder letters will be sent to rearrange the appointment.

If carers are not able to attend the face-to-face assessment appointments, or stay for the duration, they will be asked if they would be willing to complete the questionnaire booklet at home and return

it to the CTR. A Freepost self-addressed envelope will be provided for carers to return their questionnaire booklet. Alternatively, carers will be given the option of answering a short survey over the telephone, comprising some questions extracted from the questionnaire booklet.

Training for completion of trial Case Report Forms (CRFs) will be provided to the appropriate member of the research team. Data collection will be carried out by the research team which incorporates research assistants working on the trial as well as clinical studies research officer from research networks. The designated SenITA occupational therapist will answer any questions relating to the SIT.

12.5 Screening visit

Once informed consent has been obtained the researcher will:

1. Complete the sensory processing measure (Table 1).
2. Once this is complete, the researcher will be able to confirm eligibility.
3. If eligible, the participant will be immediately asked to complete a baseline assessment. If not eligible, the participant and their carer will be thanked for their interest and no further trial involvement will take place.
4. If the baseline assessment cannot take place immediately, the researchers will arrange an appointment for a convenient time.

12.6 Baseline assessment

Once screening and eligibility have been confirmed:

1. The researcher will complete the baseline measures (Table 1).
2. Once these are complete, the researcher will be able to carry out randomisation.
3. Participants and carers will be informed of their treatment allocation by the research team.
4. For those allocated to the intervention arm, the SIT therapist will contact the carer to arrange sessions for delivery of the intervention.
5. For both arms, the carer will be given access to a diary in which they will be asked to complete either online or in paper format depending on the carer's preference.
6. All carers will be reminded that there will be further follow up assessments at 6 and 12 months.

12.7 Follow up assessment

Follow up assessments (table 1) for all participants will be conducted six and 12 months after randomization with a +/- 2 weeks window.

12.8 Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."*

Table 2. Source data.

Trial data	*Source data*				
	Participant medical notes	*Participant therapy notes*	*Participant Diary*	*Electronic Case Report Form*	*SAE form*
Medical History	*X*				
Intervention delivery		*X*			
Usual care/contact with services			*X*		
Outcome measure				*X*	
Adverse events					*X*

12.8.1 Completion of CRFs

All assessments will be completed using web-based CRFs. This is a secure encrypted system accessed by username and password, and complies with Data Protection Act standards. In the event that the web-based system is not accessible, paper CRFs will be used to record data. The data will then be inputted into the web-based system once it is accessible. A full data management plan will accompany this protocol and will be stored in the TMF.

12.9 Diary completion

Carers of children in both arms will complete a diary during the intervention period (i.e. for six months following randomisation). Carers will be asked to report on both health professional contacts and any home programmes or self-initiated activities.

12.10 Qualitative data collection

Scoping focus groups with therapists: A minimum of two focus groups will be held prior to recruitment. Each will utilise a case analysis approach with clinicians providing treatment for sensory processing difficulties (one in each region). Case analysis is a method of generating an in-depth, multi-level understanding of a potentially a complex issue and is used extensively various research fields.

In the event key contributors are unable to attend a focus group, a small number of one-to-one telephone interviews may supplement focus group data. Focus groups will explore what is currently delivered/received as UC in the Health Boards/Trusts involved, and what if any difference exists in local provision and between regions (i.e. Wales and England).

In order to develop a schedule for the focus groups, a brief survey has been distributed to Occupational Therapist Practice leads (OTs) in trial regions working with the trial population, via OT service leads. Questions included: how often patients with ASD and sensory-processing difficulties were seen; what functional issues/behaviours were addressed; what advice was usually given; whether any particular theory underpinned the approach used/advice given; whether a sensory-based approach was used and in what form it takes place, and finally level of OT training in sensory-based approaches.

Interviews with carers of children with ASD and sensory processing difficulties (parents from both South Wales and Cornwall): These will utilise a time-line facilitated process. Timelining is a visual method that has been successfully used in interviews[37]. This method also has the benefit of allowing continuities and differences in usual care experiences to be highlighted by the individuals with experience during data production, rather than in data analysis by a researcher who, by necessity, has to add a lens of interpretation.

Participants will be sent a timeline template and guidance prior to the interview, but will be encouraged to tell their story in the manner that best suits them, which may involve deviating from the template. We will ask participants to focus on key points along a timeline, including 'the beginning', 'diagnosis' and 'now'. We will ask carers to identify therapies and therapists that have been engaged at various time points, and their feelings regarding whether this treatment has been supportive.

12.11 Carer and therapist interviews

Following the six-month/post-intervention time-point, diary and artefact facilitated interviews will be conducted with all SIT therapists and a sample of therapists providing UC (5-10 interviews) and a sample of carers in both arms (anticipated to be 10-15 in each arm before data saturation).

Primary carers may choose to be interviewed alone or with other members of their family who are involved in day to day care. Participants will be asked to reflect on their experience of the intervention and the usual care activities that occurred alongside it.

SIT therapist interviews will explore the following themes: barriers to implementation and facilitating factors, adherence, therapeutic relationship with the child, carer-therapist alliance, degree of adaptation required (according to ability/motivation and/or type of sensory difficulty) and perceptions of mechanisms of change. Therapists will be sampled to achieve variation in Health Board/Trust and regional centre and will be given the choice of telephone or face-to-face interviews.

Carer views (SIT arm) will be sought around barriers and facilitators to participation, the nature and severity of their child's sensory processing deficit/s, acceptability of the intervention, factors influencing adherence and use of home-based strategies and their child's engagement with activities at home and/or school. UC therapist and carer interviews will focus on contamination, specifically to explore whether UC received differs as a function of the trial. Carers in the UC arm will also be asked for their views on their child's specific sensory deficit.

In order to empower carers to tell their stories, they will be asked to bring their SenITA research diaries[38] and any other information they have gathered during the course of the interviews relating to their care, including letters from therapy providers, letters from education providers and their own records of these interactions[39]. This may include personal notes and diaries or their social media accounts – wherever they routinely describe their child's therapeutic encounters.

Participants will be directed to tell their story, but to also reflect on any impact they felt the treatment had on their lives at this time.

Carers will be sampled to ensure maximum variation in terms of range of ASD and sensory symptoms, Health Board/Trust, and regional centre. Interviews will be face-to-face, in person, given the sensitive nature of the topic to aid rapport and engender a trusting relationship in which the interviewee is able to open up and reflect on their experiences at ease. They will take place at a location of the interviewee's choice, often their home. Carers will be offered a £10 high street voucher for their participation in the interview.

The interview topic guides will be developed from a review of previous research, guides used by the research team in similar studies, and with input from the multi-disciplinary research team to avoid bias in topic selection and wording of questions. The topic guide will be piloted and refined as necessary. Interviews will be recorded and transcribed verbatim. References to identifiable personal details such as name, address, and date of birth, will be removed from the transcripts.

13 Safety reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR unless the SAE is specified as not requiring immediate reporting (see section 13.2).

13.1 Definitions

Table 3. Adverse Event definitions.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Serious Adverse Event (SAE)	Any adverse event that -

	• Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.2 Causality

Causal relationship will be assessed for the intervention (Sensory Integration Therapy) and procedures. The Principal Investigator will assess each SAE to determine the causal relationship and the Co-Chief Investigator can also provide this assessment where necessary:

Table 4. Definitions of causality.

Relationship	Description	Reasonable possibility that the SAE may have been caused by the intervention?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No

Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

13.3 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness.

There are no expected AEs/SAEs. Any planned treatments at the start of the study will not be considered as AE's/SAE's.

13.4 Reporting procedures

13.4.1 Participating Site Responsibilities

The PI should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

SenITA@Cardiff.ac.uk

SAE number: 02920 687608

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 1 month after the participant receives the intervention.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure.

13.4.2 The CTR responsibilities

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness. Where the SAE and is both related and unexpected, the Trial Manager will notify REC within 15 days of receiving notification of the SAE. All SAEs will be recorded and reported annually to the main REC. A standard template will be used to record SAEs. Following the initial report, all SAEs should be followed up to resolution

wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 1 month after the participant receives the last part of the intervention.

13.5 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

14 Statistical considerations

14.1 Randomisation

We will randomly allocate participants to usual care or SIT in a 1:1 ratio (1 participant allocated to usual care for every 1 allocated to the SIT intervention arm) using minimisation, with a random component (set at 0.8) used to allocate participants to the group that causes the least imbalance with a probability of 0.8. Allocations will be minimised by site, severity of SP difficulty (probable/definite), and sex of the child (male / female). Participants will be randomised following screening, consent and collection of baseline data. The trial statistician, in collaboration with other statisticians within the Centre for Trials Research at Cardiff University (CTR), will develop and test the randomisation programme. As it will not be possible to blind recruiters to previous allocations, and for the feasibility of intervention delivery we are having to balance allocations by site, we have aimed to reduce the risk of selection bias by not using permuted block randomisation, and rather incorporating a random element into our minimisation algorithm (so it is not completely deterministic), and by minimising by a prognostic covariate as well as by site[40].

14.2 Blinding

All data cleaning and manipulation prior to statistical analysis will be carried out blind to allocated treatment. Treatment arm will be requested following completion of this and testing of analysis syntax (using dummy randomisation data).

14.3 Sample size

We will recruit 216 participants in total (108 allocated to usual care, 108 allocated to the SIT intervention). This will provide 90% power at the 5% significance level to detect a standardised effect size of 0.5, allowing for 20% loss to follow-up.

Our effect size is based on means and standard deviations of the ABC-I in relevant populations found in the literature [15, 41, 42]. This literature also suggests that a 25% relative difference represents a clinically meaningful difference on the ABC-I. Findings from the internal pilot will aid in confirming the accuracy of the assumptions behind the sample size calculation.

14.4 Missing, unused & spurious data

Detail will be provided in the Statistical Analysis Plan (SAP).

14.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

14.6 Termination of the trial

Progression criteria for the internal pilot phase is described in section 12.1.

14.7 Inclusion in analysis

Primary and secondary analysis will primarily be based on a modified intention to treat (MITT) analysis population, which includes all participants with outcome data in the group to which they were randomised.

A full intention-to-treat (ITT) analysis set will comprise all participants in the group to which they were randomised, with missing outcome data imputed using multiple imputation. This analysis set will serve as a sensitivity analysis to the primary outcome.

Finally, a complier average causal effect (CACE) population will comprise participants with outcome data, in the group to which they were randomised, with adequate adherence (to be defined *a priori* in the Statistical Analysis Plan). This analysis set will also serve as a sensitivity analysis to the primary outcome.

15 Analysis

15.1 Main analysis

The primary analysis will be based on the MITT analysis population, and will estimate the between-group mean difference in the ABC-I at six months using linear regression, adjusting for baseline ABC-I, recruitment site, severity of SP difficulty, and sex of the child. Therapist clustering will be accounted for using mixed models, if appropriate. Secondary outcomes will be treated similarly. Secondary outcomes will be analysed similarly.

15.1.1 Sub-group & non-adherence

The impact that non-adherence to the intervention has on the ITT findings will be investigated by estimating the Complier-Average Causal Effect (CACE) for the primary and secondary outcomes[43]. While the main trial analysis will be based on a MITT analysis population, sensitivity analyses will be carried out exploring the impact that missing data may have had on trial findings. Where outcome data are missing due to drop-out/loss to follow-up, these will be assumed to be missing at random given observed data (MAR), and multiple imputation will be used to achieve a full ITT analysis population. Additional sensitivity analyses will be conducted using joint modelling approaches (e.g. selection and/or pattern mixture models) to explore departures from a MAR assumption[44]. Subgroup analyses will be conducted, exploring any differential intervention effects by site, region,

age, sex of the child, severity of SP difficulties, adaptive behaviour, socialisation, and comorbid conditions. This will be carried out by repeating the primary analysis but including each subgroup as an explanatory variable along with a subgroup x treatment arm interaction. Subgroup analyses will also be performed for adaptive functioning (child) and carer stress.

15.2 Mediation analysis

Mediation analyses will be conducted to explore whether or not any effect of the intervention on behavioural problems at one-year (all ABC subscales) is mediated through an effect on sensory sensitivities immediately post-intervention. The analyses will control for baseline measures of behavioural problems and sensory sensitivities, in order to minimise any residual confounding between mediator and outcome[45]. Additional analyses will be conducted to explore the association between measures collected as part of the process evaluation and primary/key secondary outcomes. As the majority of process evaluation measures will only be collected for participants allocated to the SIT arm, the analysis will be purely associational and therefore hypothesis generating in nature.

15.3 Exploratory analysis

Given the variability in the 'usual care' that we are likely to see, we will conduct analyses using participants in the UC arm only that explore the association between different types of usual care and clinical outcomes. Parameters we will use to characterise different types of usual care will include number of treatment contacts, therapist experience/level of training, and type of difficulty for which the therapy is intended. Regression models will be fitted using our primary and secondary outcomes, and the therapy characteristics/parameters as explanatory variables. Variables that confound the relationship between therapy characteristics and outcome (e.g. age, severity of SP difficulty, etc.) will be investigated and controlled for in the models, but the interpretation of the findings from these analyses will reflect the exploratory nature of this work and will be purely associational (that is, without ascribing cause).

A Statistical Analysis Plan will provide further detail on analytical methods using for the analysis of trial outcomes, and will be finalised prior to the end of recruitment.

15.4 Qualitative analysis

Qualitative data will be analysed by the qualitative team using thematic analysis[25]. We will search across the data set to find repeated patterns of meaning, and identify key themes and sub-themes. We will identify contradictory data, as points of contrast as well as similarities to understand uptake and engagement with the intervention. Vital measures will be put into place to ensure validity and reliability. Double coding will be carried out until consensus is reached. Data will be managed using qualitative coding software (such as NVivo10). This qualitative component has been designed using the principles of the Critical Appraisal Skills Programme qualitative checklist, to ensure the quality of qualitative research[46].

15.5 Health economic analysis

The health economic analysis will be carried out on an intention-to-treat basis. The main analyses will compare cost and cost-effectiveness at six-months follow-up of SIT compared to UC. Mean costs for the treatment groups will be analysed using regression analysis and bootstrapping. NHS and PSS costs (or societal costs in the secondary analyses) over the six-months will be regressed on treatment allocation, baseline ABC-I, site, severity of SP difficulty and baseline costs. We will account for clustering in the analysis.

To mitigate effects of data skewness, non-parametric bootstrapping methods will be used to estimate 95% confidence intervals (CIs) for mean costs. The cost-effectiveness of SIT v UC will be compared by calculating incremental cost-effectiveness ratios (ICERs), defined as difference in mean costs divided by difference in mean ABC-I. Non-parametric bootstrapping from the cost and effectiveness data will be used to generate a joint distribution of incremental mean costs and effects for the comparators to explore the probability that each is the optimal choice, subject to a range of maximum values (ceiling ratio) that a decision maker might be willing to pay for an additional ABC-I. Cost-effectiveness acceptability curves (CEAC), a recommended decision-making approach to dealing with uncertainty, will be generated by plotting these probabilities for a range of values of the ceiling ratio. Sensitivity analysis will be used to explore the sensitivity of the results from using a broader societal perspective than a narrower NHS/PSS perspective preferred by the National Institute for Health and Care Excellence (NICE) reference case[47].

16 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

17 End of Trial definition

The treatment phase will be followed by a non-interventional follow-up period which will continue for 6 months after the last participant completes protocol treatment.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as the date on which the completion of any follow-up monitoring and data collection occurs.

Sponsor must notify the main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

18 Archiving

All data will be kept for 15 years in line with Cardiff University's Research Governance Framework Regulations for clinical research. This data will be stored confidentially on password protected servers maintained on the Cardiff University Network. Files will only be accessible to researchers responsible for the running of the trial and the Chief Investigator (CI). All procedures for data storage, processing and management will comply with the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to researchers and the Chief Investigator. The Trial Statistician will carry out the analyses. All essential documents generated by the trial will be kept in the Trial Master File. Archiving and access to archive will be managed in accordance with the Standard Operating Procedures of the Centre for Trials Research (CTR).

19 Regulatory Considerations

19.1 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval. This trial protocol will be submitted through the Welsh permission system (DSCHR PCU) for global governance.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

19.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. This includes the use of video records. Data will be stored in a secure manner and will be registered in accordance with the Data Protection Act 1998. Data handling procedures will be laid out in full in the Data Management Plan.

19.2.1 Data sharing plan

Data will be collected in a suitable format to facilitate sharing when required. This will be possible via Managed Access.

19.3 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

19.4 Trial sponsorship

Cardiff University will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial. All delegated responsibilities will be detailed in a trial delegation log which will be filed in the TMF.

19.5 Funding

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 15/106/04) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

High street vouchers to the value of £10 will be offered to carers at each follow up assessment time point. Carers who take part in an interview will also be offered a £10 high street voucher. All carers allocated to the intervention arm will be eligible to submit a travel expenses claim for up to £50 at the end of the intervention period.

The trial will be adopted on the NIHR portfolio.

20 Trial management

The trial will be conducted according to CTR Standard Operating Procedures, including those for project management and trial committee structure, data management and protection, adverse/serious adverse event reporting, maintaining trial documentation according to GCP and archiving trial data. Cardiff University will act as Sponsor for the trial and study-specific SOPs will be developed as required. The planned trial committee structure is outlined below.

20.1 Project Team

Project Team: The Project Team (PT) will meet weekly and will include the CI, co-CI, Trial Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Trial Management Group (TMG).

20.2 TMG (Trial Management Group)

The TMG will meet 4-6 weekly and will include all Investigators and the trial Project Team (as detailed above) to discuss trial progression and key management issues. The Trial Manager will be responsible for day-to-day running and coordination of the trial and will be accountable to the CI. The Trial Manager will manage the workload of other staff employed directly to the study. TMG members will be required to sign up to the remit and conditions set out in the TMG Charter.

20.3 TSC (Trial Steering Committee)

Given that the intervention has been classed as low risk, there will not be a separate Data Monitoring Ethics Committee (DMEC) unless the Trial Steering Committee (TSC) deem it necessary to convene one Instead, there will be a TSC only that will meet at least annually. It will comprise of an independent Chair with expertise in trials of occupational therapy, an independent ASD expert, an independent statistician and a carer representative (parent/carer of a child with ASD and SP difficulties) with the Co-CIs, Statistician and Trial Manager as observers. The TSC will provide overall

supervision for the trial and provide advice through its independent chair. The TSC will advise NIHR whether the trial should continue following the results of the internal pilot. TSC members will be required to sign up to the remit and conditions set out in the TSC Charter.

20.4 Patient and Public Involvement (PPI)

A small advisory group comprising family carers (3-4) recruited via the National Autistic Society will be convened. We will also approach a young person (18+ years) with autism who has received a sensory-based intervention, to join the advisory group. The role of the advisory group will be to provide feedback on study materials, and advise on appropriate strategies for recruitment, retention and dissemination of results.

21 Quality Control and Assurance

21.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the SenITA trial. Low/Low+ monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

21.2 Audits & inspections

The trial is participant to inspection by the Health Technology Assessment programme (HTA) as the funding organisation. The trial may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

22 Publication policy

All publications and presentations relating to the trial will be detailed in the publication policy which will be drafted and authorised by the TMG. It will state principles for publication, describe a process for developing output, contain a map of intended outputs and specify a timeline for delivery. The publication policy will respect the rights of all contributors to be adequately represented in outputs (e.g. authorship and acknowledgments) and the trial to be appropriately acknowledged. Authorship of parallel studies initiated outside of the TMG will be according to the individuals involved in the project but must acknowledge the contribution of the TMG and the CTR.

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