BEAMS-ID

Behavioural Interventions to Treat Anxiety in Adults with Autism and Moderate to Severe Intellectual Disabilities

PROTOCOL

VERSION 1.6 – 16 NOVEMBER 2022

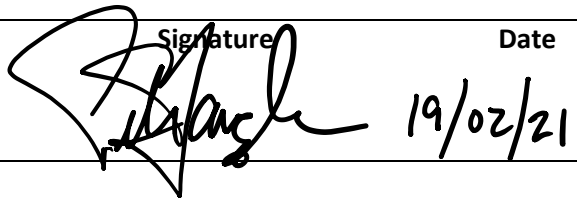
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant regulations, GCP guidelines, and relevant 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 study publicly 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.

Study Sponsor: Coventry and Warwickshire Partnership NHS Trust			
Name Dr Kay Wright	**Position Head of Research and Innovation Operations**	**Signature** 	**Date** 24/02/21
Chief Investigator:			
Name Professor Peter Langdon		**Signature** 	**Date** 19/02/21

General Information This protocol describes the Behavioural Interventions to Treat Anxiety in Adults with Autism and Moderate to Severe Intellectual Disabilities (BEAMS-ID) and provides information about the procedures for entering participants into the study. 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 study. Problems relating to the study should be referred, in the first instance, to study team.

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Study Co-ordination:

The BEAMS-ID study is being coordinated by the study team based at the University of Warwick with the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit working collaboratively with the team within an advisory role.

This protocol has been developed by the BEAMS-ID Study Management Group (SMG).

For **all queries** please contact the BEAMS-ID team through the main study email address. Any clinical queries will be directed through the Study Manager to either the Chief Investigator or Co-Investigators.

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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/AE form should be completed by the clinician and submitted to the study manager within 24 hours of becoming aware of the event (See section 16 for more details).

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Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
HTA	Health Technology Assessment
IC	Informed consent
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NLI	No Local Investigator
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality control
QL (QoL)	Quality of Life
R&D	Research and Development
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SMF	Study Master File
SMG	Study Management Group
SSG	Study Steering Group

1 Amendment History

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

Version submitted for ethics approval: 1.1.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
1	1.2	18.02.2021	Added name of the Study Manager. Added signature of the Chief Investigator and Sponsor. Added REC ref, IRAS number and ISRCTN number.
2	1.3	22.02.2021	Amended the section on TAU survey to add option of completing the survey verbally via Microsoft Teams in a form of a semi-structured interview.
3	1.4	17.01.2022	We have changed the way Adverse Events will be reported. Instead of using CRFs, site teams will be asked to use SAE/AE reporting form.
4	1.5	09.05.2022	We have changed the duration of the study from 18 months to 24 months in line with 6-month no-cost extension approved for the study.
5	1.6	31.05.2022	We have amended information on number of recruitment sites for Phase 2. This was planned to be two sites, but we have changed it to be up to 4 to accelerate accrual.
6	1.7	02.08.2022	We have amended information on number of recruitment sites for Phase 2. This was planned to be 4sites, but we have changed it to be up to 6 to accelerate accrual.

7	1.8	16.11.2022	We have changed the duration of the study from 24 months to 28 months in line with 4-month no-cost extension approved for the study.

2 Synopsis

Short title	Behavioural interventions for anxiety
Acronym	BEAMS-ID
Internal ref. no.	Ideate: 64326
Development phase	Feasibility
Funder and ref.	National Institute for Health Research - Ref: NIHR129804
Study design	Phase 1a: intervention adaptation. Phase 1b: survey of treatment as usual (TAU) within community settings. Phase 2: single-group feasibility study
Study participants	Phase 1a: our Intervention Adaptation Group (IAG) will be comprised of 6 to 8 key stakeholders who will be representatives from our PPI partners, carers and family members, people with autism and/or intellectual disabilities, and clinicians, along with members of the research team. Phase 1b: services for adults with autism and intellectual disabilities within the United Kingdom including NHS mental health and learning disabilities services, and the independent and charitable sector, including social enterprises. Phase 2: autistic adults, aged over 16 years, with a diagnosis of moderate to severe intellectual disabilities who have a diagnosis of an anxiety disorder confirmed at screening. As this group is heterogenous, we aim to purposefully sample participants to ensure that at least one third have severe intellectual disabilities.
Planned sample size	Phase 1a: 6 to 8. Phase 1b: up to 20 community teams. Phase 2: 30 individual participants
Planned number of sites	Phase 1b: up to 20 sites for survey of TAU, Phase2: up to 6 sites for recruitment of participants for intervention modelling
Inclusion criteria	Phase 2: (a) diagnosis of autism confirmed by case note review, (b) existing diagnosis of moderate to severe intellectual disabilities confirmed at screening, (c) existing diagnosis of an anxiety disorder confirmed or initially made at screening, (d) carer or family member able to support participation in the intervention, and (e) for those who do not have capacity, permission for inclusion in accordance with the Mental Capacity Act (2005).
Exclusion criteria	Phase 2: (a) currently receiving another psychological therapy for a mental health problem.
Treatment duration	Phase 2: 8 to 12 individual sessions lasting approximately 60 to 90 minutes each
Follow-up duration	Phase 2: 4 weeks
Planned study period	28 months
Objectives	To adapt an existing intervention that was developed for use with people who have autism and anxiety disorders, investigate the feasibility of implementing the intervention with 30 patients, and characterise TAU by completing a national survey of services. The objectives of our feasibility study are: (i) to model the manualised intervention to determine the acceptability and feasibility for all stakeholders, including patients, carers, and clinicians, (ii) judge the appropriateness, including response rates, of our measures of anxiety-related symptomatology for use within a larger study, (iii) examine the feasibility and acceptability of consent and associated processes (e.g. use of the

	Mental Capacity Act), (iv) describe factors that facilitate or challenge the implementation of our intervention.
Primary outcomes	Measure of symptoms of anxiety that is appropriate for use with autistic adults who have moderate to severe intellectual disabilities to be chosen by Intervention Adaptation Group.
Secondary outcomes	(a) anxiety diagnosis (e.g. a diagnostic checklist using the Diagnostic Manual - Intellectual Disability-2), (b) symptoms of autism (e.g. Social Responsiveness Scale – 2 92), (c) emotional and behaviour problems (e.g. Developmental Behaviour Checklist-2), (d) challenging behaviour (e.g. the Behavioural Problems Inventory – Short Form), (e) community outcomes (e.g. the Index of Community Involvement), (f) medication, as well as (g) conversion, accrual, attrition, and response rates on outcome assessments.
Intervention	Adapted and manualised intervention comprising 8 to 12 individual sessions of a behavioural intervention lasting approximately 60 to 90 minutes delivered by therapists trained in the treatment manual.

3 Study summary & schema

3.1 Study schema and participant flow diagram

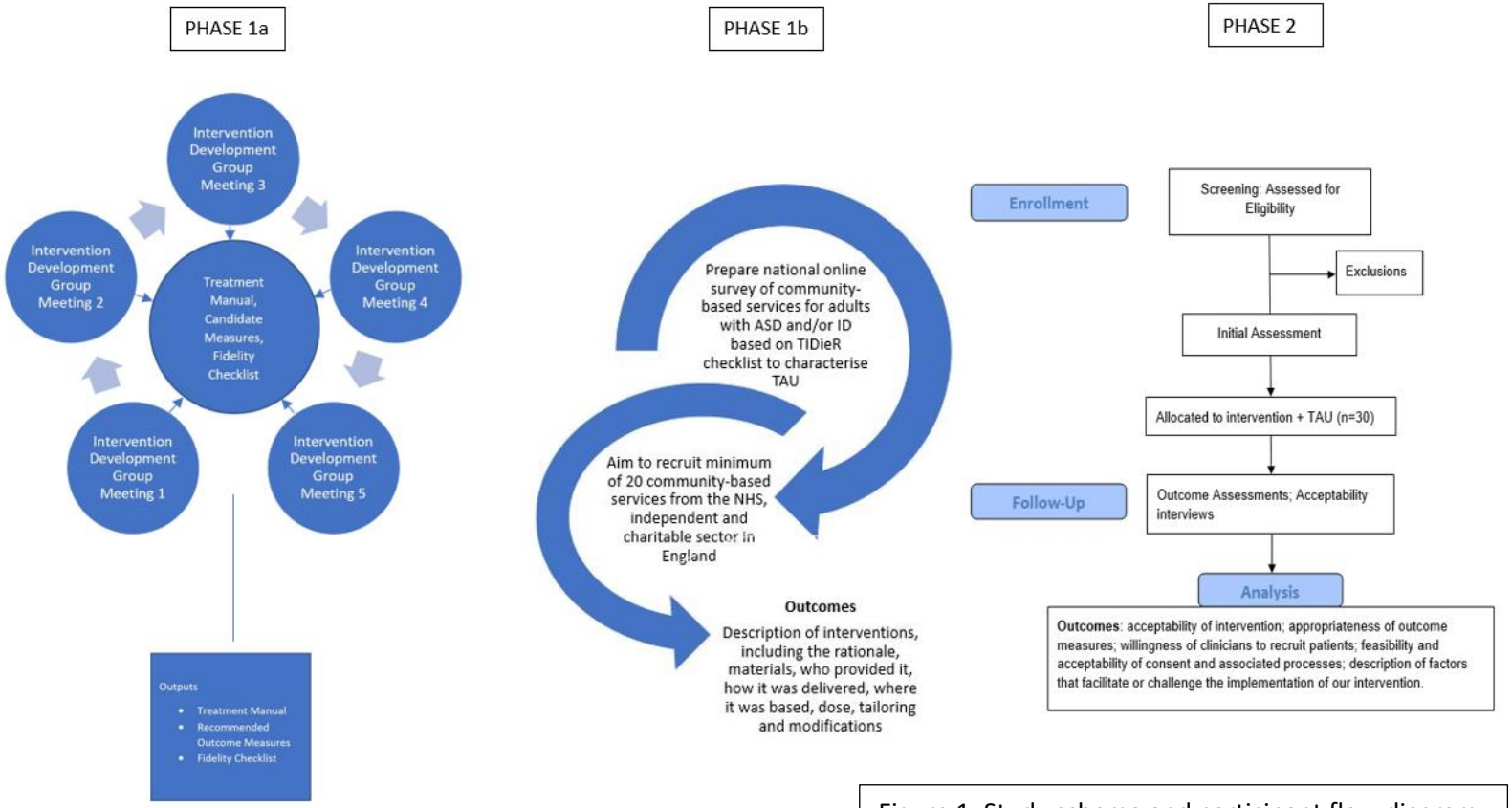


Figure 1: Study schema and participant flow diagram

3.2 Study lay summary

Background: Our study is about autistic adults who have moderate to severe intellectual disabilities, and problems with anxiety. There are good therapies for anxiety, but these have not been tried with autistic adults with moderate to severe intellectual disabilities. In order to meet the needs of autistic adults with moderate to severe intellectual disabilities, these therapies need to change.

Aims: (a) we will work with autistic adults, carers and family members, and professionals to adapt an existing therapy for anxiety disorders that was developed for autistic adults without intellectual disabilities, and (b) complete a study to try out our therapy and seek feedback from participants and their families. We will also collect information about what sort of therapy people are currently getting, along with testing out some good ways to measure anxiety.

Method: Our study has two parts. In the first part, we will change our existing therapy together with autistic adults with intellectual disabilities, parents, carers and clinicians. This work will be led by an autistic person and members of the research team. We will use something called action research methods and consensus development meetings to change our treatment and figure out the best way to measure anxiety. This means that we will repeatedly spend time with autistic adults with intellectual disabilities, parents, carers and clinicians, working together to make changes to therapy. At the same time, we will do a national survey to find out what treatments or therapies people are getting now. In our second phase, we will try out our therapy with 30 autistic adults with moderate to severe intellectual disabilities. We will also try to interview participants, carers and clinicians about their experiences of doing our study. This will help us work out whether people like the therapy, can use our measures of anxiety, and whether there is anything that we need to change to help people better.

Patient and Public Involvement: We want autistic adults with moderate to severe intellectual disabilities, carers and family members involved in our study. We are working with the National Autistic Society who will help with this study. They will help prepare our paperwork, find people to be in our study, and tell people about what we find out. We have autistic adults who will be in charge of our study with us and will help us change our therapy.

Dissemination: We will write peer review articles which are published in a journal, which is like a magazine. These are often read by professionals. To make sure many people find out about our study, the National Autistic Society help us tell people about it using their Network Autism and their Your Autism magazine. We will also make a podcast. The National Autistic Society will also tell people

about our study using social media and their website, and we will put it on our website. We will have a seminar (like a lecture) with The National Autistic Society and autistic adults will help us. We will also do a talk about our study at the National Autistic Society Professional Conference, and other conferences. If you want to know about our study, just ask us, and we will tell you.

3.3 Research Summary

Background: A large number of people with autism and intellectual disabilities have problems with anxiety. There is good evidence that talking psychological therapies are an effective treatment for anxiety, but many of these treatments have not been tested for use with people who have both autism and intellectual disabilities. These treatments need to be adapted before they can be used with this population because of their difficulties with verbal communication, restricted and repetitive behaviours and challenging behaviour.

Aims: (a) using co-production with our Patient and Public Involvement (PPI) partners, we will adapt an existing manual for the treatment of anxiety disorders amongst people with autism and intellectual disabilities, and (b) complete a feasibility study to try out our intervention and seek feedback from participants and their families. In addition, we will collect information about what treatment people are currently receiving to effectively describe current Treatment-as-Usual (TAU) and test out some outcome measures.

Method: Our study has two phases. In our first phase, we will adapt an existing treatment manual using co-production with our PPI partners, inclusive of service users, carers and clinicians. This work will be jointly led with a service user with autism and members of the research team. We will use action research methods and consensus development meetings to both adapt our intervention and appraise several candidate outcome measures that can be used within our feasibility study. At the same time, we will characterise TAU by completing a national survey of services, structured using the Template for Intervention Description and Replication (TIDieR) checklist. In our second phase, we will complete a feasibility study of our manualised intervention with 30 patients who will receive the intervention plus treatment as usual (TAU). We will interview participants, carers and clinicians about their experiences of taking part in this study. This will allow us to understand the acceptability and experience of receiving intervention, along with the suitability of outcome measures and factors that may hinder or facilitate the research.

Patient and Public Involvement: PPI is firmly and genuinely an integral part of our methodology. We have partnered with the National Autistic Society who will work with us collaboratively to use

co-production to adapt our intervention. At the same time, they will also help us prepare our study documentation, recruit participants, and collaboratively disseminate information about our study and findings. Service users, carers, and clinicians will sit on our Study Steering Group and have shared oversight of the progress of this project, while also helping lead the development of the intervention. The treatment manual to be adapted was already developed with PPI input.

Dissemination: In addition to publishing peer review articles, we will work with the National Autistic Society to maximise dissemination. This will include publishing a Network Autism and Your Autism magazine and podcast. The National Autistic Society will share information about our study and our findings with carers and stakeholders through social media and their website. We will also share information about our study and findings on our own websites. The National Autistic Society will host a seminar about our work which will be delivered jointly with PPI members, and we will deliver a talk at the National Autistic Society Professional Conference, while also disseminating our findings at other international conferences.

4 Background

There is some evidence that "talking" psychological therapies are effective for people with autism without intellectual disabilities and those with mild intellectual disabilities (Vereenooghe & Langdon, 2013; Weston, Hodgekins, & Langdon, 2016), but the evidence base for using these interventions for those with both autism and moderate to severe intellectual disabilities is limited. While there is substantial evidence that cognitive behavioural therapy is an effective treatment for anxiety disorders in adults (Hofmann & Smits, 2008), the inclusion of cognitive methods within behaviour therapy has been questioned with some demonstrating that they *do not* improve treatment outcomes (Hayes, 2004; Longmore & Worrell, 2007; Sweet & Loizeaux, 1991), including within treatments for anxiety disorders (Borkovec & Costello, 1993; Emmelkamp, Mersch, Vissia, & Van der Helm, 1985; Mattick, Peters, & Clarke, 1989; Vogel, Stiles, & Gotestam, 2004). Considering the challenges that those with autism and intellectual disabilities have with verbal communication, psychological therapies which focus more on the behavioural components of the intervention are likely to be advantageous.

Rosen et al. (Rosen, Connell, & Kerns, 2016) recently completed a systematic review of behavioural interventions used for the treatment of anxiety disorders with people who have both autism and moderate or more severe intellectual disabilities. Their review included seven studies involving children, adolescents and adults, and none were randomised control trials; all studies made use of

single case experimental designs. Within the review, a variety of behavioural interventions with adaptations, such as the inclusion of parents or carers within therapy, were successfully modelled which included: systematic desensitisation and the use of fear hierarchies (Koegel, Openden, & Koegel, 2004; Love, Matson, & West, 1990; Luscre & Center, 1996), video modelling and mastery techniques (Luscre & Center, 1996), stimulus fading (Shabani & Fisher, 2006), positive reinforcement to support behaviour change (Luscre & Center, 1996; Schmidt, Luiselli, Rue, & Whalley, 2013; Shabani & Fisher, 2006; Wolff & Symons, 2013), and exposure techniques (Allison, Harrop, & Ellett, 2013; Schmidt et al., 2013; Shabani & Fisher, 2006; Wolff & Symons, 2013). These studies suggest that behavioural interventions have the potential to be beneficial for the treatment of anxiety amongst those with autism and moderate to severe intellectual disabilities. However, our group has recently completed a systematic review of interventions for mental health problems for children and adults who have severe intellectual disabilities (including those with autism) (Vereenooghe et al., In Press). Very few studies met the eligibility criteria for inclusion, and those evaluating psychological therapies made use of minimal quality single case experimental designs – with a resulting very poor current evidence base, indicating that better modelling and feasibility studies are initially needed to inform the decision as to whether to proceed to pilot trials.

It is clear that people with autism are at increased risk of developing mental health problems, including anxiety disorders, relative to their neurotypical peers (Baird et al., 2006; Hofvander et al., 2009; Joshi et al., 2013; Simonoff et al., 2008). Those with autism often present with atypical reactions to sensory stimuli as well as restricted and repetitive interests which are associated with anxiety, including an insistence on sameness and routine (Lidstone et al., 2014; Wigham, Rodgers, South, McConachie, & Freeston, 2015). Approximately 32 to 43% of those with autism and have symptoms of anxiety (Bakken et al., 2019; Bradley, Bolton, & Bryson, 2004), while members of our research team have identified that up to 14.3% will have a diagnosis of an anxiety disorder by the age of 27, compared with only 7.1% of the general population (Nimmo-Smith et al., Submitted). Adapted talking psychological therapies can be used to treat anxiety disorders with people with have autism (Weston et al., 2016), and similar interventions can be used with people who have mild intellectual disabilities (Jahoda et al., 2017; Vereenooghe & Langdon, 2013). However, as already mentioned, the evidence to support their use with people who have autism and *moderate to severe* intellectual disabilities is sparse.

A variety of factors have been associated with the development of emotional disorders in autistic children, teenagers and adults. It is important that these factors are considered and incorporated within treatment programmes for people with autism, and include: (1) poor social functioning

(Pouw, Rieffe, Stockmann, & Gadow, 2013), and social skills difficulties (Bellini, 2004, 2006), including social motivation (Factor, Condy, Farley, & Scarpa, 2016), (2) poor friendship quality (Whitehouse, Durkin, Jaquet, & Ziatas, 2009) and lack of social support (Gotham, Bishop, Brunwasser, & Lord, 2014; Hedley, Uljarevic, Foley, Richdale, & Trollor, 2018a), (3) poor coping strategies (Pouw et al., 2013), (4) loneliness (Hedley et al., 2018a; Hedley, Uljarević, Wilmot, Richdale, & Dissanayake, 2018b; Whitehouse et al., 2009), (5) reduced awareness of difficulties (Gotham et al., 2014; Vickerstaff, Heriot, Wong, Lopes, & Dossetor, 2007), (6) seeing oneself as dissimilar from others (Hedley & Young, 2006), (7) rumination (Crane, Goddard, & Pring, 2013; Gotham et al., 2014), (8) traits of autism (Hedley et al., 2018a), (9) lack of flexibility and associated executive function difficulties, which has been associated with anxiety (Hollocks et al., 2014; Wallace et al., 2016), (10) difficulties with meta-cognition, which has been associated with depression (Wallace et al., 2016), (11) restricted and repetitive behaviours (Magiati et al., 2016; Spiker, Lin, Van Dyke, & Wood, 2012; Wigham et al., 2015), including an insistence on sameness (Black et al., 2017; Gotham et al., 2013; Lidstone et al., 2014; Rodgers, Glod, Connolly, & McConachie, 2012; Uljarevic, Lane, Kelly, & Leekam, 2016; Wigham et al., 2015), (12) intelligence (Dubin, Lieberman-Betz, & Michele Lease, 2015; Mazurek & Kanne, 2010; Niditch, Varela, Kamps, & Hill, 2012; Weisbrot, Gadow, DeVincent, & Pomeroy, 2005), which has not been consistently associated with emotional disorders in some studies (Moss, Howlin, Savage, Bolton, & Rutter, 2015), (13) sensory issues, including atypical sensory over-responsivity and avoidance of sensory input (Black et al., 2017; Green & Ben-Sasson, 2010; Green, Ben-Sasson, Soto, & Carter, 2012; Lidstone et al., 2014; Wigham et al., 2015), intolerance of uncertainty (Boulter, Freeston, South, & Rodgers, 2014; Maisel et al., 2016; Neil, Olsson, & Pellicano, 2016; Vasa, Kreiser, Keefer, Singh, & Mostofsky, 2018; Wigham et al., 2015), which has been shown to mediate the relationship between sensory issues and anxiety, as well as anxiety and insistence on sameness (Hwang, Arnold, Srasuebkul, & Trollor, 2019), and (15) alexithymia (Maisel et al., 2016).

People with autism and moderate to severe intellectual disabilities who have anxiety disorders have a high level of need, and this has been recognised by the NHS. In 2015 (NHS England, 2015), *Building the Right Support* was published which is a national plan for England to develop community services for people with intellectual disabilities and/or autism in an attempt to reduce the need for hospital admission. As part of this new national service model for people with intellectual disabilities and/or autism, all individuals should be offered both mainstream and specialist NHS health care, including mental health treatments, as needed. While there are well-developed evidence-based psychological

therapies for the general population, such an evidence base does not exist for people with autism and moderate to severe intellectual disabilities. The results of our recent systematic review of interventions for mental health problems in individuals with severe intellectual disabilities, including those who have autism, found no robust evidence for any psychological intervention approaches for anxiety (39). Thus, individuals with autism and moderate to severe intellectual disabilities face an evidence inequity whereby there is a lack of research information to guide treatment despite significant levels of need. However, NICE does recommend psychological interventions, including relaxation training and exposure therapy, for adults with either autism or intellectual disabilities who have mental health problems (National Institute for Health and Care Excellence, 2012, 2015, 2016).

Lifetime care costs for one person with autism and intellectual disabilities have been estimated at £1.5 million (Buescher, Cidav, Knapp, & Mandell, 2014), while the literature about the economic benefits of healthcare interventions for autistic people with intellectual disabilities is sparse. Developing mental health interventions for people with autism was recently identified as the number one priority by stakeholders, including people with autism and their families in the James Lind Alliance priority setting exercise (http://www.jla.nihr.ac.uk/news/answering-the-questions-from-people-with-autism-their-families-and-health-professionals/7681). NHS England have recently identified autism and intellectual disabilities as a 10 Year Plan clinical priority for the NHS, while the need to eliminate any potential discrimination against those with a protected characteristic, as defined within the Equality Act, 2010, has been recognised by NHS England (NHS England, 2017) within their published research plan for the NHS. This has also included a recommendation that research must reduce health inequalities amongst patients, which is directly relevant to patients with autism and moderate to severe intellectual disabilities who face a double inequality (existing health inequalities coupled with a lack of evidence about how best to reduce these).

However, developing and testing interventions for this population is associated with several challenges and feasibility studies are needed to effectively model these challenges and develop effective solutions. First, individuals with autism and intellectual disabilities have significant communication difficulties. Second, there is an increased prevalence of challenging behaviour (e.g. aggression, self-injurious behaviour) amongst this population (Cooper et al., 2009; Holden & Gitlesen, 2006) which may not be recognised as associated with a mental health problem (Deb, Thomas, & Bright, 2001a, 2001b) especially in those with more severe intellectual disabilities (Painter, Hastings, Ingham, Trevithick, & Roy, 2018), but needs to be considered in the context of treatment for anxiety. Third, those with autism present with restricted and repetitive behaviours (Magiati et al., 2016; Spiker et al., 2012; Wigham et al., 2015), an insistence on sameness (Black et

al., 2017; Gotham et al., 2013; Lidstone et al., 2014; Rodgers et al., 2012; Uljarevic et al., 2016; Wigham et al., 2015), sensory over-responsivity and avoidance of sensory input (Black et al., 2017; Green & Ben-Sasson, 2010; Green et al., 2012; Lidstone et al., 2014; Wigham et al., 2015), and rumination (Crane et al., 2013; Gotham et al., 2014), amongst other difficulties (Hedley et al., 2018a) related to autism which need to be considered within treatment. Fourth, a large proportion of this population are unlikely to have capacity to provide informed consent to take part in research. As such, the provisions of the Mental Capacity Act (2005) in England and Wales must be followed. Fifth, the measurement of anxiety symptomatology within the context of a future clinical trial requires consideration, including the appropriateness of patient reported outcome measures (PROMS) in this population.

Considering measurement, our group has also recently completed a systematic review of measurement tools for mental health problems with people who have severe or profound intellectual disabilities, including those who also have a diagnosis of autism (Flynn et al., 2017). The measures deemed to be the most robust overall in terms of available data were both broad-based psychopathology tools: the Aberrant Behaviour Checklist (Aman & Singh, 1986), and the Diagnostic Assessment for the Severely Handicapped Scale-II (DASH-II; Matson, 1995). Specific data on the measurement of anxiety in this population were more limited. Thus, some work is required to determine the most appropriate measures to use within a clinical trial of behaviour therapy for anxiety in people with autism and moderate to severe intellectual disabilities.

Taking the aforementioned issues together, the current project aims to adapt and model a manualised intervention for the treatment of anxiety disorders amongst people with autism who have moderate to severe intellectual disabilities within a feasibility study. We will use co-production to adapt an existing treatment programme (Doble et al., 2017; Langdon et al., 2016; Langdon et al., 2013), complete a survey of treatment within existing services to characterise TAU, and complete a feasibility study to model the intervention. This project will draw on mixed methods and comprise two phases detailed below.

5 Study objectives

Aim

To adapt an existing intervention that was developed for use with people who have autism and anxiety disorders, investigate the feasibility of implementing the intervention with 30 patients, and characterise TAU by completing a national survey of services.

5.1 Objectives

Phase 1a (Intervention Adaptation)

Our objectives are:

(i) to establish an intervention adaptation group (IAG), and using co-production during a series of meetings, adapt an existing intervention used within a previous clinical trial to treat anxiety symptoms in adults with autism (Doble et al., 2017; Langdon et al., 2016; Langdon et al., 2013) for use with people who also have moderate to severe intellectual disabilities,

(ii) to develop a treatment fidelity checklist that can be used alongside the treatment manual, and

(iii) to appraise and consider several candidate outcome measures of anxiety-related symptoms and social care, and make a recommendation for use within Phase 2.

Phase 1b (TAU Survey)

(i) Our objective is to complete a national survey of existing interventions for adults with anxiety disorders who have moderate to severe intellectual disabilities, which will include items adapted from the Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014) to ensure clear description of TAU. See the Appendix for description of the items that form the TIDieR checklist. This phase will run concurrently with Phase 1a and Phase 2. This will allow us to capture and characterise TAU effectively, including any specific interventions offered. We aim to invite participation from all community-based services for people with autism and/or intellectual disabilities across the United Kingdom.

Phase 2 (Feasibility Study)

Our objectives are:

(i) to model the manualised intervention to determine the acceptability and feasibility for all stakeholders, including patients, carers, and clinicians, and adjust as required,

(ii) judge the appropriateness, including response rates, of our measures of anxiety-related symptomatology for use within a larger study,

(iii) examine the feasibility and acceptability of consent and associated processes (e.g. use of the Mental Capacity Act)

(iv) describe factors that facilitate or challenge the implementation of our intervention.

5.2 Outcomes

Key outcomes of this study will be: description of TAU (UK-wide); adaptation and manualisation of an existing intervention; likely design of a future trial including outcome measures, and a logic model based on assessment of the following primary feasibility outcomes: (i) recruitment (ii) reach (e.g. are we able to recruit those with severe ID), (iii) adherence: session attendance, (iv) retention (withdrawal and loss to follow up and outcome measure completion rates) rates, (v) acceptability (vi) description of factors that facilitate or challenge the implementation of our intervention, and (vi) feasibility and acceptability of consent and associated processes.

We will also decide likely primary and secondary outcome measures for use within a future trial. A likely outcome measure will be an instrument which captures symptoms of anxiety and is appropriate for use with participants who have both autism and intellectual disabilities. This choice of measure will be decided following our work during Phase 1 of this project, and then further tested within Phase 2. Our group has recently completed a systematic review of measurement tools for mental health problems with people who have severe or profound ID, including those who have co-morbid autism (Flynn et al., 2017). The measures deemed to be the most robust overall in terms of available data were the Aberrant Behaviour Checklist (Aman & Singh, 1986) and the Diagnostic Assessment for the Severely Handicapped Scale-II (DASH-II; Matson, 1995) and these will be taken to our IAG for consideration. However, these two measures are general psychopathology tools and specific data on the measurement of anxiety in this population were more limited. Thus, the IAG will determine the most appropriate measures to use within our feasibility study which will be completed within Phase 1a.

The IAG will consider a range of secondary outcome measures that could also be used within a future trial that will also be tested further within Phase 2, for example: (a) anxiety diagnosis (e.g. a diagnostic checklist using the Diagnostic Manual - Intellectual Disability-2) (National Association for the Dually Diagnosed, 2016), (b) symptoms of autism (e.g. Social Responsiveness Scale – 2) (Constantino et al., 2003), (c) emotional and behaviour problems (e.g. Developmental Behaviour Checklist-2 Adult (DBC2-A)) (Gray, Tonge, Einfeld, Gruber, & Klein, 2018), (d) challenging behaviour

(e.g. the Behavioural Problems Inventory – Short Form) (Mascitelli et al., 2015; Rojahn et al., 2012), and (e) community outcomes (e.g. the Index of Community Involvement) (Raynes, 1994).

We will also collect information about medication at baseline and post-intervention to test the feasibility of capturing this information. This information will be collected from carers and corroborated with prescribing clinicians as required. Any changes will be recorded and noted. We will also record and report data on accrual rates, attrition, response rates in relation to our measures. At this stage, we are not considering incorporating measures of quality of life or resource use as this would be incorporated into a future pilot trial.

For our outcome instruments, we will examine the percentage of participants and carers who complete them at each time point, the percentage of items within each outcome measure for each participant that are completed, and the percentage who judge our outcome measures to be acceptable.

6 Study design and setting

Phase 1a (Intervention Adaptation)

We will establish an Intervention Adaptation Group (IAG) comprised of 6 to 8 key stakeholders who will be representatives from our PPI partners, carers and family members, people with autism and/or intellectual disabilities, and clinicians, along with members of the research team. This group will be led by a person with autism who has a history of difficulties with anxiety together with members of the research team. We will use co-production, and working together with stakeholders, we will use action research over a series of *five meetings over four months* to: (a) define the needs and problems that are to be addressed for people with autism and moderate to severe intellectual disabilities, (b) define the intervention objectives, with reference to the likely barriers, (c) adapt the existing manualised intervention, develop the fidelity checklist, and consider candidate primary and secondary outcome measures, including measures of social care, making a recommendation for use within Phase 2, (e) consider any additional methods to identify users of the intervention, clarification of how to measure outcomes, and further development of implementation protocols as needed, and (f) further consideration of any challenges or barriers to our evaluation plan, including likely to solutions, coupled with the decision as to how to measure outcomes.

A logic model will be developed, feedback will be sought at each meeting, and following reflection, subsequent refinements will be made to the manual and fidelity checklist by the research team which will be presented to the IAG at the next meeting leading to a final version. This will ensure

that our approach is problem-focused and cyclical, allowing for repeated episodes of reflection and action during and between meetings (Leykum, Pugh, Lanham, Harmon, & McDaniel, 2009).

We will make use of our existing intervention that was previously developed for the treatment of anxiety disorders amongst people with autism who do not have intellectual disabilities (Doble et al., 2017; Langdon et al., 2016; Langdon et al., 2013), and adapt it for use with those who have moderate to severe intellectual disabilities by focusing on the behavioural components. This is because many of the patients will have marked difficulties with verbal communication because they have moderate to severe intellectual disabilities and are not able to take part in traditional "talking" psychological therapies. The existing intervention was also developed with strong PPI input from adults with autism and their parents as part of a previously funded NIHR grant (RfPB: PB-PG-1208-18024).

Our previously developed modularised intervention (Langdon et al., 2016; Langdon et al., 2013) included the following modules: (a) psychoeducation about anxiety and autism, (b) cognitive-based interventions for anxiety, (c) social skills training, (d) relaxation training, (e) building fear hierarchies, (f) exposure therapy and systematic desensitisation, and (g) behavioural experiments.

During Phase 1 of this project, we aim to focus upon the following modules: (a) relaxation training, (b) building fear hierarchies, (c) exposure therapy and systematic desensitisation, and (d) behavioural experiments for use with those who have both autism and moderate to severe intellectual disabilities. This intervention has previously been tested within a successful pilot trial with patients with autism who have anxiety disorders (Doble et al., 2017; Langdon et al., 2016; Langdon et al., 2013).

The outcomes from Phase 1 will be: (a) logic model, (b) an adapted intervention manual that can be tested within a feasibility study, (c) a fidelity checklist, and (d) candidate outcome measures for use within our feasibility study.

Phase 1b (TAU Survey)

Design. This will be a survey of existing community-based services within the United Kingdom to characterise TAU which will be offered online or verbally via Microsoft Teams. Our survey will include questions that are informed by the Template for Intervention Description and Replication (TIDieR) checklist. The TIDieR checklist is used to provide a description of an intervention, including the use of any associated materials. Who, how and where an intervention is delivered is also described as well as the associated dose and modifications. Our online survey will be delivered using

Qualtrics. There will be an option to complete the survey verbally via Microsoft Teams with a member of the research team. This will be in a form of a semi-structured interview using the same questions as the online survey.

Setting. All services for adults with autism and intellectual disabilities (and intellectual disabilities services providing support to those who also have autism) within the United Kingdom will be invited to take part in this study with an aim of recruiting at least 20 community teams; this includes NHS mental health and learning disabilities services, and the independent and charitable sector, including social enterprises. We will make use of our Research in Developmental Neuropsychiatry (RADiANT) consortium of NHS providers and our existing network of twenty-nine NHS Trusts and private sector providers who participated in the mATCH study (RfPB: PB-PG-0214-33040) to help ensure successful recruitment. RADiANT is a consortium of NHS service providers which works in collaboration with academics in a number of universities. It seeks advice from service users, patients, families, charities, community leaders and a range of statutory bodies and organisations. RADiANT focuses on mental health and behavioural issues associated with five developmental conditions- intellectual disabilities, autism, attention deficit hyperactivity disorder, epilepsy and acquired brain injury. It is hosted by Hertfordshire Partnership University NHS Foundation Trust (HPFT), and multiple NHS Trusts are partners who have committed to actively supporting and taking part in research studies within the aforementioned five developmental conditions, including the lead NHS Trust for the current application, Coventry and Warwickshire Partnership NHS Trust. Worcestershire Health and Care NHS Trust are an additional partner in this project and a full member of RADiANT.

Phase 2 (Feasibility Study)

*Design***.** We will make use of our existing treatment manual, which will have been adapted within Phase 1 of the current study, and complete a feasibility study to model the behavioural intervention and determine its acceptability and feasibility for stakeholders including service users, carers and clinicians who are delivering the intervention in according with the MRC Framework for developing and assessing the feasibility of complex interventions (Medical Research Council, 2006; O'Cathain et al., 2019). Further refinements to the manual are anticipated.

We will include a single-arm non-randomised feasibility study of behavioural intervention plus TAU for the treatment of anxiety disorders amongst people with autism who have moderate to severe intellectual disabilities, and the use of qualitative and quantitative research methods to help address key components of feasibility. Recruitment will be open to participants with autism and moderate to severe intellectual disabilities who have anxiety disorders within England. We anticipate that family or paid carers will actively be involved in treatment in some capacity (extent and nature of

involvement to be determined during Phase 1 of the research). Treatment will be delivered by trained therapists (e.g. nurses, assistant psychologists, allied health professionals) who work with people with autism and intellectual disabilities who have received additional training in the behavioural intervention. Participants will be assessed at three times points: (1) screening, (2) assessment within 4-weeks before the commencement of the intervention, and (3) assessment within 4-weeks of the completion of the intervention.

Setting, Context, and Study Pathway. The study will take place within NHS mental health and learning disabilities services in England (Coventry and Warwickshire Partnership NHS Trust; Worcestershire Health and Care NHS Trust, and other Trusts if necessary, to reach recruitment targets). We will nest our project within the RADiANT consortium of NHS providers working in collaboration with a number of universities. We will make use of this network to help facilitate the timely recruitment and participants into this study. For the current project, we will use a multi-point recruitment strategy incorporating specialist community teams for people with autism or intellectual disabilities, advocacy and family support groups, mental health teams, the voluntary and charitable sector, special education settings that include young adults (some schools, special education colleges), self-referral, and through our PPI partners associated networks, specifically the National Autistic Society. The steps in the pathway for the feasibility study are as follows: (a) all participants who provide consent, or participants where a Consultee, in accordance with the Mental Capacity Act, 2005, has provided advice that the participant can be included, will be screened by research staff to ensure they meet the eligibility criteria for the study, (b) following baseline assessment, participants who meet eligibility criteria will be assigned to receive the behavioural intervention plus TAU, and we aim to provide the treatment within existing services within our sites, (c) participants who receive the behavioural intervention plus TAU will have regular scheduled contact with a therapist, and we have allocated between 8 to 12 *individual* sessions of the intervention per participant within our current timetable, (d) participants will then be assessed using our outcome measures within 4-weeks following the completion of the intervention, (e) a subsample of participants and their carers and clinicians will be asked to take part in semi-structured interviews following the intervention process to further ascertain acceptability and the experience of the intervention the study pathway, and procedures, consent, and associated factors to create a description of factors that promote or challenge the implementation of the intervention, recognising that those with severe intellectual disabilities may not be able to take part in these interviews, meaning that we will have to rely on carers and family members, and (f) through the Study Steering

Committee, make a recommendation to the funders for their consideration as to whether a future clinical trial is feasible. This decision will be made by the funder once the study results are available.

6.1 Risk assessment

A Study Risk Assessment has been completed to identify the potential hazards associated with the study 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 study has been categorised as low risk, where the level of risk is comparable to standard care. A copy of the study risk assessment may be requested from the Study Manager. The study risk assessment is used to determine the intensity and focus of monitoring activity (see Section 25.1).

7 Site and investigator selection

This study will be carried out at participating sites within the United Kingdom. All sites who are interested in participating in the study will be required to confirm capability and capacity to host the study to ensure they have adequate resources and experience to conduct the study.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the BEAMS@warwick.ac.uk study email account (see contact details on page 4):

- Confirmation of capacity and capability in line with the information provided in the initial assessment letter and/or HRA approval letter.
- Authorised Organisational Information Document (Non-Commercial) with completed local details.
- 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 Sheet(s) and Consent Form(s) on host care organisation headed paper

Upon receipt of all the above documents, the Study Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the centre is now ready to recruit participants into the study. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive all the documents required to recruit into the study.

Occasionally during the study, amendments may be made to the study documentation listed above. The study team will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the study team to ensure that new documents have the associated correct approvals.

Site initiation will be by tele- or videoconference if attendance of key personnel in person is unfeasible.

8 Participant selection

Participants are eligible for Phase 2 of the study if they meet all the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Study Manager.

8.1 Inclusion criteria

- diagnosis of ASD confirmed by case note review
- existing diagnosis of moderate to severe intellectual disabilities, confirmed at screening
- existing diagnosis of an anxiety disorder confirmed or initially made at screening
- carer or family member able to support participation in the intervention (assuming this is one of the key adaptations incorporated)
- for those who do not have capacity, permission for inclusion in accordance with the Mental Capacity Act (2005)

8.2 Exclusion criteria

- currently receiving another psychological therapy for a mental health problem

9 Recruitment, screening, and registration

9.1 Participant identification

We will use a multi-point recruitment strategy incorporating specialist teams for people with autism, and intellectual disabilities services also supporting individuals with an additional diagnosis of autism, advocacy and family support groups, mental health teams, the voluntary and charitable sector, special education services supporting young people 16 years+, self-referral, and members from our PPI partners, specifically the National Autistic Society, including carers and family members. Participants will be identified through all these routes, and information about the study will be placed within the public domain upon our website and the National Autistic Society website.

Where eligible participants need to be identified prior to consent being taken, screening will be conducted by clinicians who routine access to personally identifiable information (e.g. nursing staff working within a community teams for people with intellectual disabilities and/or autism). This initial screening will take place only within the NHS and may involve a search of patient records or discussion with clinician teams. The personally identifiable information required for screening is diagnosis which will be taken from clinical records, specifically a diagnosis of autism and moderate to severe intellectual disabilities and information to suggest that the person has problems with anxiety and whether they are already receiving psychological therapy. This will be checked by a clinician outside of the study team who will then share information about the study with participants and/or carers.

Clinicians will then share information about Phase 2 of this study with likely eligible participants and/or carers. Participants and/or carers will then have contact with the study team via two possible routes:

(a) Participants and/or carers tell clinicians that they want their contact details passed to the study team when asked. The study team will receive the details from clinicians and then contact the participants and/or carers.
(b) Participants and/or carers contact the study team directly using the contact information they were provided.

There is a third route which is for those participants and/or carers who are identified via the voluntary, charitable sector and education, or for those who self-refer:

(c) Participants and/or carers will have contacted the study team directly using contact information they would have seen on websites or within adverts (e.g. information within newsletters or emails sent to the membership of a charity).

The research team will take responsibility for definitive screening to determine eligibility.

9.2 Screening logs

A site screening log of all ineligible and eligible but not consented/not approached will be kept at each site to monitor accrual. Logs will not contain identifiable information. The screening log should be sent to BEAMS@warwick.ac.uk every month (see section 19 for further detail on data monitoring/quality assurance).

A study screening log will be kept by the study team who will complete definitive screening. Again, this is to monitor accrual and ensure that participants are screening into the study effectively.

9.3 Recruitment rates and Retention

Our overall planned accrual rate is 5-6 participants per month over five months to reach our aim of a final sample size of up to 30. We will make use of multiple strategies to promote retention that have proved successful in our previous NIHR research studies, including: (a) maintaining regular contact with participants, and minimising the time between contacts, (b) promoting service-user involvement at all stages of the study, (c) using co-production to develop the intervention to help encourage retention, (d) working effectively with the charitable sector to help encourage continued engagement, and (e) we anticipate that the active inclusion of carers and/or family members within treatment may increase retention within both therapy and the research process.

9.4 Consent

Phase 1a and 1b: Participant care is paramount within this study, and our procedures for gaining consent to include someone within this study will be completed before enrolment. Our participant information sheets are laid out in an easier-to-read format and can be adapted further to meet the individual needs of participants if and as required (e.g. additional use of aids to support communication and understanding).

Seeking informed consent will be the responsibility of a member of the research team. We will seek consent to retain pseudonymised data for use within future studies. It is unlikely that any of our participants enrolled to take part in Phase 1a or 1b will lack capacity to decide whether they wish to take part in this part of the study.

For Phase 1a, participants will be working collaboratively with the research team, and these meetings are likely to take place virtually. We will seek permission to record these sessions from participants. For Phase 1b, participants will be asked to provide consent using an online form. If participants decide to complete the survey verbally via Microsoft Teams, we will also seek their permission to record the meeting.

The participant's written informed consent will be obtained using the correct Consent Form, which follows the Participant Information Sheet. The participant will be given up to 72 hours after the initial invitation to participate before being asked to sign the Consent Form should they wish. Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study. Consent may be taken by a member of the research team, or for Phase 1b, participants will be able to provide consent online which will be received by the research team.

Please note, only when written informed consent has been obtained from the participant and they have been enrolled into the study can they be considered a participant.

One copy of the consent form will be made available to participant, but the original copy will be digitised as soon as possible and keep within the electronic investigator site file. The original source copy will be stored within a locked filing cabinet within a secure locked room at the University.

The right of the participant to refuse to participate in the study without giving reasons will be respected.

Phase 2: While the assumption is made that all participants will have capacity to make a decision as to whether they wish to take part in this study, it is likely that many will not have capacity to make this decision within Phase 2. Therefore, the requirements of the Mental Capacity Act, 2005 must be met. The capacity to decide whether someone would like to take part in this study is determined with reference to whether they are able to understand the study, understand the consequences of taking part or refusing to take part in the study, their ability to weigh, retain, and use information about the study, and their ability to communicate a decision about taking part in the study. The current study fulfils the definition of intrusive research as defined within the Act as it is clinical research into an adapted form of treatment, and we will collect personal data.

This research project is about an impairing condition that affects participants; namely, anxiety experienced by adults with autism and moderate to severe intellectual disabilities. While the assumption that all our participants will have capacity decide if they want to take part in this study, it is the case we will be recruiting participants who have severe intellectual disabilities, and therefore, there is an increased probability that a proportion of our participants will not have capacity to make a decision about taking part in this study. It is not possible to successfully complete this project with

only those who are likely to have capacity to decide whether they wish to take part in this study for the following reason:

- This project is specifically about adapting and modelling an intervention for people with autism who have moderate to severe intellectual disabilities who are more likely to not have the capacity to decide whether they wish to take part in this study. We know little about psychological interventions to treat anxiety amongst this group. We know already that psychological treatments for mental health problems amongst those without developmental disabilities are helpful (Stewart & Chambless, 2009), and there is evidence that psychological treatments for mental health problems amongst those with autism and/or mild intellectual disabilities, who are likely to have capacity to make a decision about taking part in a research study, are also helpful (Vereenooghe & Langdon, 2013; Weston et al., 2016). However, there is little in the way of robust evidence to support the use of adapted psychological interventions for the treatment of mental health problems amongst those with more severe developmental disabilities and this is a focus of this project.

The current study is concerned with the treatment of anxiety amongst adults with autism who have moderate to severe intellectual disabilities and how treatment needs to be adapted to meet their needs because of the nature and degree of their impairing condition. This means that the research is about an impairing condition that affects our participants. While this study does not aim to attempt to ascertain the efficacy of the treatment, there is a probability that participants may potentially benefit from the treatment. Our risk assessment suggests that risk is proportionate and acceptable.

Participant care is paramount within this study, and our procedures for gaining consent or permission to include someone within this study will be completed before enrolment. Our participant information sheets are laid out in an easier-to-read format and can be adapted further to meet the individual needs of participants as required (e.g. additional use of aids to support communication and understanding).

A summary of the process and steps to be taken when seeking consent or advice from either a personal or nominated consultee for those who are judged to lack capacity to make a decision about participation is found within Figure 2.

The participant's written informed consent must be obtained using the correct Study Consent Form, which follows the Participant Information Sheet. The participant should be given up to 72 hours after the initial invitation to participate before being asked to sign the Consent Form. Informed consent

must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study. Consent will taken from participants by a member of the research team.

Similarly, a consultee's advice that a participant should be included or excluded must be obtained using either the Personal or Nominated Consultee Declaration Form which follows the Information for Personal or Nominated Consultees Information Sheet. The Consultee should be given up to 72 hours, or longer, if requested, after the initial invitation to provide advice about whether the participant should be included within this research study. Signed advice to include a participant must be obtained from the Consultee prior to the participant undergoing procedures that are specifically for the purpose of the study. Advice from consultees will be taken by a member of the research team.

A copy of the consent form or Consultee Declaration form should be given to the participant or Consultee as appropriate, but the original copy should be digitised and added to the electronic investigator site file. The source data will be stored within a locked filing cabinet within a secure locked room at the University.

The right of the participant or Consultee to refuse to participate in the study without giving reasons will be respected. A participant will remain free to withdraw, and a Consultee will remain free to withdraw a participant at any time from the treatment and/or study without giving reasons and without prejudicing his/her further treatment. It is possible for a participant or their Consultee to discontinue treatment; if such occurs, data can be collected about the participant are per protocol as if they had continued to receive treatment should they wish.

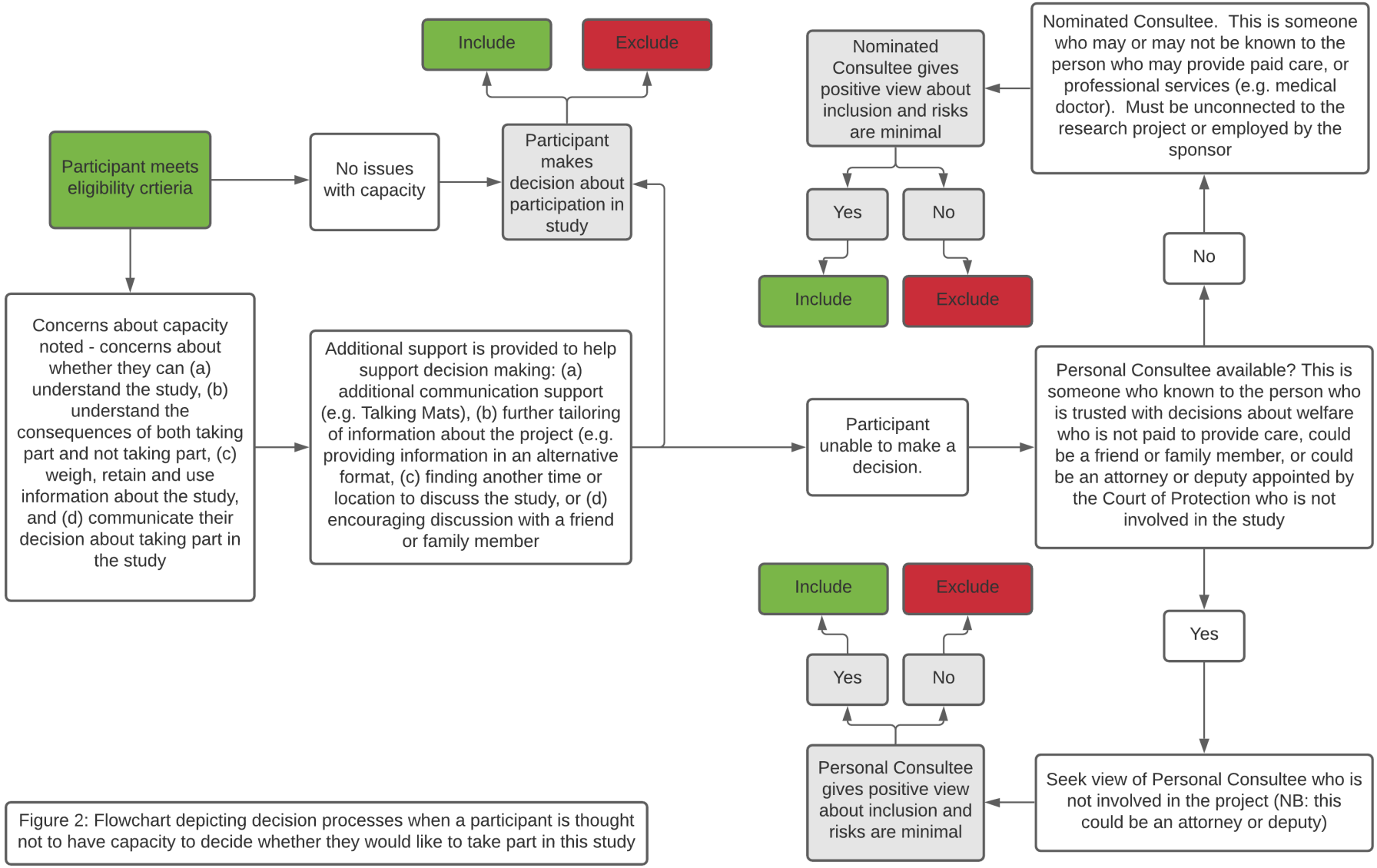


Figure 2: Flowchart depicting decision processes when a participant is thought not to have capacity to decide whether they would like to take part in this study

9.5 Registration

This study will be registered with ISRCTN Registry.

9.6 COVID-19 Mitigation

There are risks associated with the COVID-19 pandemic for this study. For Phase 1a and 1b, risk to either participants or the study team because of taking part in this study or carrying our any procedure associated with this study is minimal. The reason for this is that both Phase 1a and 1b will take place online using either video-conferencing or online survey methods.

Phase 2 poses greater risk as there is likely to be planned contact between members of the study team, health care professionals, participants, and their family members. However, as this study will take place in the NHS, and will be delivered by NHS clinicians, any wider COVID-related risk mitigation strategies in operation within NHS Trusts will apply to this study, the study team, and any therapist working as part of the study. This is likely to involve the use of Personal Protective Equipment and/or increased use of video conferencing or telephone calls. Delivering treatment solely using video conferencing or telephone calls is likely to prove problematic considering the participant population and the associated treatment, but risk mitigation strategies such as these will be discussed and implemented as recommended by the Intervention Adaptation Group in collaboration with the research team with Phase 1a. We are likely to enter Phase 2 of this study in June 2021, and a further appraisal of any associated risk associated with the COVID pandemic will need to be carried out nearer this date.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

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

If a participant initially consents but subsequently withdraws from the Phase 2, clear distinction must be made as to what aspect of the study the participant is withdrawing from; for example, it is possible to withdraw from the intervention, data collection (or part of data collection), or other aspects of the study without withdrawing completely from participation within the study. This will be clarified as best as possible with each participant and recorded. For Phase 1a and 1b, it is more difficult for participants to withdraw from individual aspects of the study, while remaining involved in the overall

phase. For example, no longer wishing to take part in the Intervention Adaptation Group would lead to complete withdrawal from this Phase of the study. Similarly, no longer wishing to take part in our survey would lead to complete withdrawal from Phase 1b. Withdrawals from Phase 1a and 1b will be recorded.

The withdrawal of participant consent within any Phase shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent, or advice from a Consultee for Phase 2, before withdrawal.

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 Phase 2 of the study, or a Consultee would like to withdraw someone from Phase 2 of the study completely, they may need to be seen one last time for an assessment depending upon the circumstances associated with the withdrawal.

In all instances participants who consent and subsequently withdraw should complete a withdrawal form or the 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 BEAMS@warwick.ac.uk. Any queries relating to potential withdrawal of a participant should also be forwarded to BEAMS@warwick.ac.uk.

10.2 Lost to follow up

For Phase 2, a participant will be recorded as lost to follow-up if the following are met:

(1) They have not responded to three attempts to schedule an appointment for either assessment or treatment, where at least one of these attempts was sending a letter to their home asking them to contact the research team, or

(2) They have not attended at least three scheduled and consecutive appointments for either assessment or treatment and have not responded to a letter sent to their home asking them to contact the research team following the third scheduled and consecutive appointment.

For those who do not adhere to the treatment protocol within Phase 2, we will collect data as per the protocol.

For Phase 1a, lost to follow-up will not be defined considering the nature of the project; participants are working collaboratively with the research team to adapt the intervention and it is anticipated that there will be little to no loss of participants. For Phase 1b, where participants are asked to respond to a survey, there is no follow-up period, and therefore, this is also not defined.

11 Study Intervention

11.1 Behaviour Therapy

11.1.1 Theoretical Framework. Contemporary learning theories provide a robust explanation of both the aetiology and treatment of anxiety disorders, through the process of direct and vicarious learning experiences. Integral to these theories is not only the process by which anxiety is learned (i.e. classical, operant and vicarious conditioning), but also the important role of vulnerabilities to anxiety such as previous vicarious conditioning, individual genetic differences, previous and future life experience, cultural and familial transmission of fears, controllability, behavioural inhibition, interoceptive conditioning (i.e. internal states becoming a 'trigger' for anxiety), and exteroceptive conditioning (i.e. external stimuli becoming a 'trigger' for anxiety) (Dunsmoor & Paz, 2015; Dymond & Roche, 2009; Grupe & Nitschke, 2013; Hofmann, 2008; Mineka & Zinbarg, 2006). These factors impact upon the experience of stressful events, which are further moderated by the predictability and perceived controllability of events, and previous direct and vicarious learning experiences. Both interoceptive (e.g. sensory input) and exteroceptive (e.g. external stimuli) conditioned stimuli can moderate stress, leading to an increase or decrease in anxiety and the quality of associated anxiety, including the intensity of any conditioned association. Events that occur post-conditioning moderate anxiety further, and these can include unconditioned stimulus inflation (factors that promote anxiety), and derived relationship responding and stimulus generalisation (where related stimuli become conditioned due to their relationship with other conditioned stimuli). Further, multiple excitatory stimuli occurring within close proximity can lead to summation effects, further increasing anxiety. Other post-conditioning events serve to moderate anxiety through their inhibitory effects, such as safety seeking behaviours and avoidance, which paradoxically maintain anxiety.

These learning processes will lead to the development of an anxiety disorder in some individuals, as depicted in Figure 1, which was adapted from Mineka and Zinbarg (Mineka & Zinbarg, 2006) to incorporate additional factors relevant to autistic people and those with intellectual disabilities (e.g. sensory over-responsivity; lack of flexibility; restricted interests; cognitive ability, communication difficulties). Clinical interventions must reflect theory, and primarily, these interventions are based upon psychological formulations using these models to inform individualised exposure techniques to

Figure 1: As depicted, contemporary learning theory postulates that anxiety disorders develop as a consequence of direct and vicarious learning experiences which are affected by a variety of factors including pre-existing vulnerabilities, the predictability and controllability of stressful events, and temporal proximity to stressful events. Additional factors such as sensory sensitivity, intellectual disabilities, restricted and repetitive behaviours, and lack of flexibility are markedly relevant for those with autism and moderate to severe intellectual disabilities. Further, the experience of anxiety is moderated by events that occur post-learning; for example, the nature and degree of avoidance behaviours, generalisation of anxiety, and additional stimuli which inflate or decrease anxiety, and directly inform interventions such as exposure therapy.



successfully treat the symptoms of anxiety, making use of strategies such as systematic desensitisation and fear hierarchies, leading to habituation or, in other words, a reduction in experienced anxiety over time.

There is some evidence drawn from single case experimental designs that interventions based upon learning theory using exposure-based interventions and associated strategies may be effective for those with autism and intellectual disabilities (Rosen et al., 2016). Exposure-based interventions have been shown to be effective for a range of anxiety disorders amongst those without autism and/or intellectual disabilities including social anxiety, specific phobias, obsessive-compulsive disorder, panic disorder, agoraphobia, and post-traumatic stress disorder (Deacon & Abramowitz, 2004; Hofmann & Smits, 2008). The exclusion of cognitive-strategies, which are delivered using verbal communication within "talking" therapy, and a reliance upon exposure-based techniques does not lead to a reduction in effect size (Hofmann & Smits, 2008; Longmore & Worrell, 2007; Sweet & Loizeaux, 1991). Considering this, psychological interventions which are not entirely delivered using verbal communication are likely to be advantageous when used with autistic adults with moderate to severe intellectual disabilities because it is not possible for many individuals to

engage effectively within "talking" psychological therapy due to their difficulties with verbal communication and processing.

11.1.2 Description of the Intervention

Participants within this study will receive between 8 and 12 sessions of individual behaviour therapy lasting between 60 to 90 minutes each. We will make use of our existing intervention that was previously developed for the treatment of anxiety disorders amongst people with autism who do not have intellectual disabilities (Doble et al., 2017; Langdon et al., 2016; Langdon et al., 2013), and adapt it for use with those who have moderate to severe intellectual disabilities by focusing on the behavioural components. Our previously developed modularised intervention (Langdon et al., 2016; Langdon et al., 2013) included the following modules: (a) psychoeducation about anxiety and autism, (b) cognitive-based interventions for anxiety, (c) social skills training, (d) relaxation training, (e) building fear hierarchies, (f) exposure therapy and systematic desensitisation, and (g) behavioural experiments. This intervention requires further adaptation because many of the patients will have marked difficulties with verbal communication associated with moderate to severe intellectual disabilities and are not able to take part in traditional "talking" psychological therapies. Adaptations will focus on the parameters of communication that are relevant to improved receptive and expressive skills and include: communicative modalities to augment speech (e.g. manual signing, graphic symbols); morpho-syntax (sentence structure, grammatical markers); vocabulary (concepts and meanings); and communicative functions. The existing intervention was also developed with strong PPI input as part of a previously funded NIHR grant (RfPB: PB-PG-1208-18024).

During Phase 1 of this project, we aim to focus upon the following modules: (a) relaxation training, (b) building fear hierarchies, (c) exposure therapy and systematic desensitisation, and (d) behavioural experiments for use with those who have both autism and moderate to severe intellectual disabilities. This intervention has previously been tested within a successful pilot trial with patients with autism who have anxiety disorders (Doble et al., 2017; Langdon et al., 2016; Langdon et al., 2013).

A description of each of these modules and their associated content is found within Table 1.

Table 1: Behavioural interventions within our existing treatment manual to be adapted for use with those with moderate to severe intellectual disabilities.

Module	Content
Relaxation	Patients are taught about the relationship between relaxation and anxiety. A variety of relaxation techniques are taught and practiced ranging from Jacobson(Jacobson, 1943) muscle relaxation to breathing exercises. Patients are encouraged to try different methods

	and choose one they consider the most beneficial. Patients are encouraged to practice relaxation out of session and assigned associated homework and record forms. Patients are asked to record the frequency and length of time they took to practice each relaxation episode, along with the associated type, and their emotional state.
Building Fear Hierarchies	Collaboratively, patients work with the therapist to break down anxiety-provoking situations into a number of different components, ranking them from least to most fearful. Multiple fears and associated fear hierarchies can be chosen. The role of safety-seeking behaviours and avoidance is explained and discussed.
Exposure Therapy and Systematic Desensitisation	These concepts are explained and the importance of using relaxation techniques while undertaking exposure therapy is discussed. Patients work through their hierarchy of fears, considering each step and how to apply relaxation strategies during exposure work. Initially, exposure techniques using imagery based-methods are used where patients begin with the least fearful step within their fear hierarchy and make use of relaxation techniques. This is repeated leading to a reduction in anxiety. Patients are asked to practice these skills outside of the session.
Introduction to Behavioural Experiments	Patients review their out-of-session skills practice using their fear hierarchies, and the paradoxical role of safety-seeking and avoidance behaviours is further discussed and considered. *In vivo* exposure work is introduced, discussed and planned collaboratively with the patient and therapist. Patients are asked to continue to practice imagined exposure and the use of relaxation techniques.
Behaviour Experiments	Over a series of sessions, the planned *in vivo* exposure work is carried out based upon the previously created fear hierarchy working from the least to the most feared situation. Patients are asked to continue to practice these techniques outside of the formal session throughout the week using their fear hierarchies and relaxation techniques.

The modules described within Table 1 will need to be adapted in ensure they are appropriate for use with those who have autism and moderate to severe intellectual disabilities and are flexibly delivered with appropriate support to meet the needs of this population, including a likely role for carers. Our adapted treatment will primarily be exposure-based anxiety treatment, which involves gradual exposure to a feared stimulus along a continuum or hierarchy of fears from the least to the most feared, while discouraging patients from using escape or avoidance behaviours as described above. This work will take place within Phase 1 of our study, and our adaptations will be consistent with the recommendations made by the National Institute for Health and Care Excellence Quality Standard (National Institute for Health and Care Excellence, 2017) which states that psychological interventions must be tailored to the preferences, level of understanding, and strengths and needs of people with intellectual disabilities. The National Institute for Health and Care Excellence Guideline (National Institute for Health and Care Excellence, 2016) for mental health problems in people with

learning disabilities provides specific guidance on the domains that should be considered when adapting psychological therapies for use with this population. These include ensuring that interventions: (a) are tailored to individual preferences, level of understanding, strengths and needs, (b) consider physical, neurological, cognitive, sensory and communication needs, (c) are respectful of privacy, (d) include family members and carers who work collaboratively with therapists, which could include helping with the provision of support outside of sessions, helping to build fear hierarchies, and the practicing of new skills, and (e) changes to the frequency and intensity of sessions, which are again tailored to meet the needs of individuals. These same NICE guidelines also specifically recommend the use of relaxation training and graded exposure techniques for the treatment of anxiety amongst people with intellectual disabilities.

These domains and associated adaptations will be presented to the IAG which will include: (a) appropriate augmented communication strategies (e.g. Signalong: www.signalong.org.uk) and graphic symbols (e.g. photosymbols: www.photosymbols.com) to support language processing and the co-construction of meaning, as well as Talking Mats (www.talkingmats.com) to support processing and decision-making; one of our co-applicants (Dr Karen Bunning) is a Speech and Language Therapist and an expert within this area. As these patients have both autism and intellectual disabilities, we will use concrete vocabulary in favour of abstract concepts, (b) ensuring appropriate support and information for carers and family members, (c) the inclusion of carers and families within treatment, including their involvement in practicing skills outside of sessions, (d) dealing with challenging behaviour and restricted and repetitive behaviour, including sensory processing difficulties, (e) changes to the frequency and intensity of sessions, and (f) appropriate strategies to deal with distress as a consequence of exposure. We anticipate that people with autism who have comorbid intellectual disabilities will need carer or supporter involvement to enhance generalisation of skills learned during therapy into everyday life. Skills/learning generalisation is a core component of all behavioural interventions, and our team have extensive experience in supporting skills generalisation for people with autism and intellectual disabilities. Treatment will be delivered by trained therapies who work with people with autism and/or intellectual disabilities who have received additional training in our manualised intervention.

11.2 Fidelity

Therapists will use a self-report fidelity checklist (a part of the manual) at the end of each session to report on, and provide data about adherence, and supervisors will be encouraged to use this checklist with their supervisees. This will be developed within Phase 1 of this study. We will look to design our fidelity checklist such that it captures both the delivery of specific components of our intervention,

and which adaptations are made by therapists when tailoring the interventions to meet the individual needs of participants (e.g. using a checklist to record the adaptations made to each session from a set of pre-existing choices). Our project team has experience of developing robust fidelity ratings for psychological interventions for people with intellectual disabilities within large clinical trials (Flynn et al., 2017; Jahoda et al., 2018) and we will use this experience to help develop our checklist for this feasibility study collaboratively with our partners within Phase 1 of the research.

We anticipate that the fidelity checking process will have two foci. First, a checklist will be developed to assess the delivery of each component in the manualised treatment (delivered, partially delivered, fully delivered). Therapists will complete a version of this checklist after each treatment session inclusive of the adaptations used. We will also ask participants and carers for permission to audio record all sessions and randomly select a session for each participant to be subjected to independent fidelity assessment to determine adherence to the manual. This will be undertaken by a research assistant. The assessment of fidelity will use a version of the checklist of the content of the manualised treatment delivery. In addition, non-specific aspects of the therapy will be coded from the recordings to address fidelity to the therapeutic process included in the manual, training and supervision. These ratings of relationship and other non-specific therapy factors will be based on a tool developed and tested in our recent trials involving people with intellectual disabilities (Jahoda et al., 2018).

12 Study procedures

Phase 1a: This part of the study will last six months. We will use co-production, and working together with stakeholders, we will use action research over a series of *five meetings over four months* to: (a) define the needs and problems that are to be addressed for people with ASD and moderate to severe intellectual disabilities, (b) define the intervention objectives, with reference to the likely barriers, (c) adapt the existing manualised intervention, develop the fidelity checklist, and consider candidate primary and secondary outcome measures, including measures of social care, making a recommendation for use within Phase 2, (e) consider any additional methods to identify users of the intervention, clarification of how to measure outcomes, and further development of implementation protocols as needed, and (f) further consideration of any challenges or barriers to our evaluation plan, including likely to solutions, coupled with the decision as to how to measure outcomes. During the periods of time between meetings, the research team will make revisions and act in response to the feedback given by the IAG. Each meeting with the IAG may last up to two

hours, inclusive of time for breaks and will be held online using Microsoft Teams to mitigate any risk associated with the current COVID-19 pandemic. A logic model will be developed, feedback will be sought at each meeting, and following reflection, subsequent refinements will be made to the manual and fidelity checklist by the research team which will be presented to the IAG at the next meeting leading to a final version. This will ensure that our approach is problem-focused and cyclical, allowing for repeated episodes of reflection and action during and between meetings (Leykum et al., 2009).

Phase 1b: This phase is a survey of all services for adults with autism and intellectual disabilities in the United Kingdom and will last for up to 14 months, running concurrently with Phase 1a and Phase 2. We are aiming to recruit 20 community-based teams and invite them to respond to a survey, either online or verbally via Microsoft Teams, which include questions that are informed by the Template for Intervention Description and Replication (TIDieR) checklist. The TIDieR checklist is used to provide a description of an intervention, including the use of any associated materials. Who, how and where an intervention is delivered is also described as well as the associated dose and modifications. Our online survey will be delivered using Qualtrics. There will be an option to complete the survey verbally via Microsoft Teams with a member of the research team. This will be in a form of a semi-structured interview using the same questions as the online survey. Example questions include, "Please provide the name or phrase that describes the intervention offered", "What are the key elements that are essential to the intervention?", "What materials are used in the intervention, including those given to participants or used in the delivery or training in the intervention?", "Who provides the intervention?". Our participant information sheets and consent forms for Phase 1b will be presented as part of our survey. Respondents are expected to provide information on a single occasion.

Phase 2: Participants are expected to be enrolled in the study for approximately 6 months. Participants will be assessed at three times points: (1) screening, (2) assessment within 4-weeks before the commencement of the intervention, and (3) assessment within 4-weeks of the completion of the intervention. Participants who meet eligibility criteria will be assigned to receive the behavioural intervention plus TAU, and we aim to provide the treatment within existing services within our sites. A subsample of participants and their carers and clinicians will be asked to take part in semi-structured interviews following the intervention process to further ascertain acceptability and the experience of the intervention the study pathway, and procedures, consent, and associated factors to create a description of factors that promote or challenge the implementation of the

intervention, recognising that those with severe intellectual disabilities may not be able to take part in these interviews, meaning that we will have to rely on carers and family members.

The assessments that are to be completed within 4-weeks prior to the commencement of treatment are our measures that captures symptoms of anxiety and is appropriate for use with participants who have both autism and moderate to severe intellectual disabilities (e.g. Aberrant Behaviour Checklist (Aman & Singh, 1986) or the Diagnostic Assessment for the Severely Handicapped Scale-II (DASH-II; Matson, 1995). Secondary measures to be completed within 4-weeks prior to the commencement of treatment include: (a) anxiety diagnosis (e.g. a diagnostic checklist using the Diagnostic Manual - Intellectual Disability-2(National Association for the Dually Diagnosed, 2016), (b) symptoms of ASD (e.g. Social Responsiveness Scale – 2 (Constantino et al., 2003), (c) emotional and behaviour problems (e.g. Developmental Behaviour Checklist-2 Adult (DBC2-A) (Gray et al., 2018), (d) challenging behaviour (e.g. the Behavioural Problems Inventory – Short Form (Mascitelli et al., 2015; Rojahn et al., 2012), (e) medication, and (f) community outcomes (e.g. the Index of Community Involvement (Raynes, 1994). A clear final decision about these assessments will be made following the completion of Phase 1a of this study. Assessment within 4-weeks after the *completion* of the intervention will be identical to that which occurs within 4-weeks prior to the commencement of the intervention.

Training and Supervision. All therapists and supervisors will be required to take part in a two-day training course in the delivery of our intervention. Therapists will receive regular supervision as part of this study from qualified clinical psychologists working within services for people within intellectual disabilities who are also trained in the intervention. This will be at least two-weekly. These supervisors will receive regular supervision from members of the research team which will also be two-weekly.

Fidelity. Therapists will use a self-report fidelity checklist (a part of the manual) at the end of each session to report on, and provide data about adherence, and supervisors will be encouraged to use this checklist with their supervisees. This will be developed within Phase 1 of this study. We will look to design our fidelity checklist such that it captures both the delivery of specific components of our intervention, and which adaptations are made by therapists when tailoring the interventions to meet the individual needs of participants (e.g. using a checklist to record the adaptations made to each session from a set of pre-existing choices). Our project team has experience of developing robust fidelity ratings for psychological interventions for people with intellectual disabilities within

large clinical trials (Flynn et al., 2017; Jahoda et al., 2018) and we will use this experience to help develop our checklist for this feasibility study collaboratively with our partners within Phase 1 of the research.

We anticipate that the fidelity checking process will have two foci. First, a checklist will be developed to assess the delivery of each component in the manualised treatment (delivered, partially delivered, fully delivered). Therapists will complete a version of this checklist after each treatment session inclusive of the adaptations used. We will also ask participants and carers for permission to audio record all sessions and randomly select a session for each participant to be subjected to independent fidelity assessment to determine adherence to the manual. This will be undertaken by a research assistant. The assessment of fidelity will use a version of the checklist of the content of the manualised treatment delivery. In addition, non-specific aspects of the therapy will be coded from the recordings to address fidelity to the therapeutic process included in the manual, training and supervision. These ratings of relationship and other non-specific therapy factors will be based on a tool developed and tested in our recent trials involving people with intellectual disabilities (Jahoda et al., 2018).

12.1 Assessments

Data will be collected by members of the research team, except for the therapists rated fidelity checklist which will be completed by therapists themselves and returned to the study team.

A schematic diagram (Figure 3) illustrates the study timelines for participants for Phase 2 only.

Figure 3. Schedule of enrolment, interventions and assessments[1]

Procedures	**Number of Visits**			
	Screening	**Baseline**	**Treatment Phase**	**Follow Up**
Informed consent or advice from a Consultee	1			
Demographics	1			
Medical history	1			
Eligibility assessment	1			
Delivery of intervention			12	
Fidelity			12 (therapist completed)	
Anxiety symptoms		1		1
Anxiety Diagnostic Checklist		1		1
Autism Symptoms		1		1
Emotional and Behavioural Problems		1		1
Challenging Behaviour		1		1
Medication		1		1
Community Involvement		1		1
Adverse event assessments (if required)			1	1
Semi-structured interviews				1

[1] Taken from the HRA CTIMP protocol template (2016).

12.2 Follow-up

There is only a single follow-up period for this study which is within 4-weeks of the completion of the intervention. For participants who discontinue treatment, and wish to remain enrolled in the study, data will be captured as per protocol. This means that data will be captured within the 4-week period following when treatment would have been completed had the participant continued to take part in the intervention.

We will carry out semi-structured interviews with up to one third of patients and their carers as well as all clinicians delivering the intervention (up to n = 10) to ascertain acceptability and the experience of the treatment, the study pathway, and procedures, consent, outcome measures used, views about randomisation within a larger trial, and integrate this information to create a description of factors that promote or challenge the implementation of the intervention with reference to our logic model.

13 Safety reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this study are familiar with the content of this section. This section applies only to Phase 2 of the study.

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

13.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or study participant administered an intervention 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***
Serious Adverse Reactions (SARs)	Any SAE occurring in a study participant for which there is a reasonable possibility that it is related to the intervention.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the intervention.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the studyl 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

The Principal Investigator (or another delegated qualified member of the trial team) will assess each SAE to determine the causal relationship and the Chief Investigator (or another appropriately qualified member of the Trial Management Group) can also provide this assessment where necessary:

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 intervention	No

Unlikely	There is little evidence to suggest there is a causal relationship with the intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). 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 intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). 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.

SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the protocol is considered unexpected.

Expected Events

Anxiety and/or distress	Participants are expected to experience some anxiety and/or distress associated with engagement within treatment. This could be of a nature and degree such that a treatment session must be discontinued to prevent further escalation of anxiety and/or distress. Should this happen, a graded hierarchy of fears governing exposure work would be expanded such that any associated anxiety and/or distress is lessoned. Anxiety and/or distress are expected to occur when the participant is not engaged within a treatment session with a therapist.
Challenging behaviour	There may be a temporary increase in challenging behaviour associated with some exposure work. This should not be of a nature or degree such that others or an individual is placed at serious risk of harm. Challenging behaviours are expected to occur when the participant is not engaged within a treatment session with a therapist.

13.4 Reporting procedures

13.5.1 Participating Site Responsibilities

The PI (or delegated appropriately qualified member of the study team team) should sign and date the SAE/AE Reporting Form (see Appendix) to acknowledge that they have performed the seriousness and causality assessments. Investigators should also report SAEs to their own Trust in accordance with local practice and this may involve the completion of an additional form.

A completed SAE/AE form for all events requiring immediate reporting should be submitted via email to BEAMS@warwick.ac.uk within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether the events had the same date of onset.

The participant will be identified only by participant number, partial date of birth (mm/yy) 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 study team 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) and Adverse Event (AE) email address:

BEAMS@warwick.ac.uk

Serious adverse events and all other adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 40 days after the participant has stopped receiving the intervention.

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

- Full participant 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 study team within 24 hours.

13.5.2 The study team responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the study team. Follow up information must be provided on a new SAE/AE form.

The study team will continue reporting SAEs until 40 days after the participant receives the last part of the intervention.

Once an SAE is received by a member of the study team, evaluated, and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Only reports of related and unexpected Serious Adverse Events (SAEs) will be submitted to the REC. These should be sent within 15 days of the Chief Investigator becoming aware of the event. There is no further requirement for annual safety reports in addition to the information provided through the annual progress report.

13.7 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 participants 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.

14 Statistical considerations

14.3 Sample size

Phase 1a: We will establish an Intervention Adaptation Group (IAG) comprised of 6 to 8 key stakeholders who will be representatives from our PPI partners, carers and family members, people with autism and/or intellectual disabilities, and clinicians, along with members of the research team. These participants will work with use to adapt and refine our intervention, measures, and fidelity checklist. There are no research data for formal analyses being collected from these participants.

Phase 1b: We will collect data about TAU from a minimum of 20 community-based services.

Phase 2: We will recruit up to 30 participants in total. As this is a feasibility study, and the purpose is to provide estimates of key parameters to inform a future pilot trial rather than to power the current study to detect statistically significant differences, a formal a priori power calculation will not be conducted (Arain, Campbell, Cooper, & Lancaster, 2010). However, recruiting 30 participants will provide reasonable precision around our estimates of parameters; for example, if 80% of participants complete the intervention, a sample size of 30 participants will allow us to calculate a 95% confidence interval around this estimate to within +/- 14.5% (i.e. from 65.5 to 94.5%). These data can be used to inform the design of any future pilot trial, provide adequate information about our candidate outcome measures, and allow us to try the intervention with important sub-groups (i.e. moderate *vs* severe intellectual disabilities) capturing the diversity of this population, much of which will be investigated using qualitative methods.

14.7 Progression criteria

This study will estimate key parameters for a future trial, which will then be used (1) to determine whether the funder advertises for a future trial and (2) to assist potential applicants in designing a future trial. We suggest the following criteria could be used to determine the feasibility of a future trial within the following domains: (a) recruitment, (b) protocol adherence, and (c) outcome data leading to three possible recommendations for trial progression (Avery et al., 2017).

Green. If all of the following criteria are met, the Study Steering Committee (SSC) will consider a recommendation that a pilot or internal pilot--full trial is warranted: (a) Recruitment: (i) accrual rate is at least 3 patients per site per month on average, and (ii) attrition rate is 30% or lower, (b) Protocol adherence: (i) fidelity ratings indicate therapist adherence to the intervention of at least 70%, (ii) at least 70% of carers and clinicians report that the intervention and consent procedures were acceptable, (iii) participants received an average of 70% or more treatment sessions, and (c) Outcome data: (i) at least 70% of participants and carers complete outcome data at each time point, (ii) at least 75% of items within each outcome measure for each participant are complete, and (iii) at least 70% of carers judge our outcome measures to be acceptable.

Amber. If any of the following criteria are met, then the research team will examine the reasons for this, carefully consider what remedial action can be taken to improve the likelihood that a larger trial should take place, and provide this analysis to the SSC for consideration. For example, difficulties may be related to a delay in research ethics or governance approvals or a longer than expected time to build relationships with referrers which could be managed effectively within a larger trial: (a) Recruitment: (i) accrual rate is less than 3 but greater than 2 patients per site per month on average, or builds up to 3 per month in the latter months of recruitment and (ii) attrition rate is greater than 30% but less than 50%, (b) Protocol adherence: (i) fidelity ratings indicate therapist adherence to the intervention is less than 70% but greater than 60%, (ii) less than 70% but greater than 55% of carers and clinicians report that the intervention and consent procedures were acceptable, (iii) participants received an average of less than 70% but greater than 55% or more treatment sessions, and (c) Outcome data: (i) less than 70% but greater than 60% of participants and carers complete outcome data at each time point, (ii) less than 75% but greater than 60% of items within each outcome measure for each participant are complete, and (iii) less than 70% but greater than 65% of carers judge our outcome measures to be acceptable.

Red. If any of the following criteria are met, and following a thorough review of the reasons for this, including consideration as to whether remedial action could be taken, a recommendation to not proceed to a larger trial may be made by the SSC: (a) Recruitment: (i) accrual rate is less than 2

patients per site per month on average, and (ii) attrition rate is greater than 40%, (b) Protocol adherence: (i) fidelity ratings indicate therapist adherence to the intervention is less than 50%, (ii) less than 55% of carers and clinicians report that the intervention, and consent procedures were acceptable, (iii) participants received an average of less than 55% or more treatment sessions, and (iv) less than 60% of participants received their allocated intervention, and (c) Outcome data: (i) less than 50% of participants and carers complete outcome measures at each time point, (ii) less than 50% of items within each outcome measure for each participant are complete, and (iii) less than 65% of carers judge our outcome measures to be acceptable.

All recommendations will be made to the SSC, including our analysis of associated barriers and proposed remedial action.

15 Analysis

15.1 Main analysis

As this is a feasibility study, the analysis will be descriptive in nature. Continuous data will be reported as means and standard deviations, or medians and interquartile ranges, as appropriate, along with their associated 95% confidence interval over time. Categorical data will be reported as frequencies and proportions. No formal hypothesis testing will take place. The study will be reported in accordance with the CONSORT extension for randomised pilot and feasibility studies (Eldridge et al., 2016). All data analysis will receive quality assurance checks from a senior statistician within Cardiff CTU.

15.2 Qualitative analysis

We will use Framework analysis to analyse the data generated from our semi-structured interviews with carers, participants and clinicians. Framework analysis is a pragmatic method which is advantageous within this context because it allows researchers to investigate key issues of interest, rather than analyse data for emergent themes. Specifically, we will use framework analysis to examine the views of participants, carers, and professionals on several key areas as outlined above within the section about semi-structured interviews.

16 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." There is only one set of source data at any time for any data element, as defined in site source data agreement. The location of source data is depicted within the following Table:

Study data	Source Data					
	Qualtrics	CRF	Participant medical notes	SAE/AE Form	Semi structured interviews	Therapist checklist and audio recordings
Phase 1b						
Description of TAU	x				x	
Phase 2						
Diagnosis of autism and intellectual disabilities, and anxiety			x			
Concurrent Medications		x	x			
Adverse events				x		
Primary Outcome		x				
Anxiety Diagnostic Checklist		x				
Autism Symptoms		x				
Emotional and Behavioural Problems		x				
Challenging behaviour		x				
Community involvement		x				

Data about acceptability and the experience of the treatment, the study pathway, and procedures, consent, outcome measures used, views about randomisation within a larger trial					x	
Fidelity						x

16.1 Data collection

16.2 Completion of CRFs

16.2.1 Paper CRFs

In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility, and timeliness of the data reported in the CRFs. Completed CRFs should be returned to the study team and will be checked for missing, illegible or unusual values (range checks) and consistency over time. If missing or questionable data are identified, a data query will be raised with the site. The site shall be requested to respond to the data query. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The study team will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

17 Protocol/GCP non-compliance

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

18 End of Study definition

The treatment phase will be followed by a 4-week follow-up period. This will continue until the last participant completes the intervention and the final outcome assessment within this 4-week follow-up period.

The end of the study is defined as the date of final data capture to meet the study endpoints. In this case end of study is defined as the date that the last participant completes the intervention and the final outcome assessment within the 4-week follow-up period having also completed any associated semi structured interviews.

The sponsor must notify the main REC of the end of a study within 90 days of its completion or within 15 days if the study is terminated early.

19 Archiving

The Study Master File and Study Site File contain essential documents that will be archived by the sponsor for a minimum of 10 years digitally. This will include copies of signed documents that have been digitised (e.g. delegation logs).

20 Regulatory Considerations

20.1 Ethical and governance approval

This protocol has a favourable ethical opinion from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval, and approval from the Health Research Authority.

20.2 Data Protection

The study team 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. Data will be stored in a secure manner and in accordance with the General Data Protection Regulation 2016. The data custodian for this study is Coventry and Warwickshire Partnership NHS Trust.

20.3 Indemnity

- Non-negligent harm: This study is an academic, investigator-led and designed study, coordinated by the study team with support from Cardiff CTU. The Chief Investigator, local Investigators and

CTU do not hold insurance against claims for compensation for injury caused by participation in a study and they cannot offer any indemnity.

- Negligent harm: Where studies are carried out within an NHS Trust, the Trust continues to have a duty of care to a participant being treated, whether the participant is participating in this study. Coventry and Warwickshire Partnership NHS Trust does not accept liability for any breach in another Trusts duty of care, or any negligence on the part of employees of other hospitals. 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 study (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.

20.4 Study sponsorship

Coventry and Warwickshire Partnership NHS Trust will act as the sponsor for this study. Responsibilities will be delegated to sites as listed within the delegation log. Other responsibilities will be delegated to the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement.

20.5 Funding

This study is adopted on the NIHR portfolio and is funded by the National Institute for Health Research – Health Technology Assessment awarded to Professor Peter Langdon, University of Warwick and Coventry and Warwickshire Partnership NHS Trust.

21 Study management

Study Steering Committee. A study steering committee (SSC) will be established who will meet three times throughout the duration of the project. The SSC will be comprised of four to five independent members, including an independent Chair and statistician. Our members will be

chosen in such a way as to ensure that we have a representative group of appropriate stakeholders, including experts, service users and carers. The SSC will have a supervisory responsibility for the entire project, not only the study. The chief investigator and study manager will attend as observers. The independent chair of the SSC is Professor Jan Burns.

Study Management Group. The study management group will comprise of the chief investigator and all co-applicants, including study delivery team (i.e. study manager, statistician, administrator). This group will meet 6-weekly to setup the study, monitor progress and deal with issues as they arise, paying particularly attention to timescales.

Project Team. The study manager will be responsible for organising weekly project team meetings with the study team using video and audio-conferencing facilities, inclusive of the chief investigator. This group will deal with the day-to-day running of the project and will report to the study management group.

The committees, groups and teams will make use of video conferencing facilities, as necessary.

22 Quality Control and Assurance

22.1 Monitoring

Study related monitoring, including audits, by providing direct access to source data/documents as required may be required. Participant consent for this will be obtained. Findings generated from any on-site and any central monitoring will be shared with the Sponsor, Chief Investigator, Principal Investigator, and local Research Governance department.

22.2 Audits & inspections

The study is participant to inspection by NHS Research Governance departments. The study may also be participant to inspection and audit by Coventry and Warwickshire Partnership NHS Trust under their remit as Sponsor.

23 Publication policy

A publication is defined as a research paper published in a peer review journal, presentations inclusive of posters, at conferences, and other material detailing the methods or findings using data obtained from participants during this study placed in the public domain (e.g. websites, book chapters).

The roles of various members of the research team for ensuring that publications are effectively manged are detailed below:

(a) Chief Investigator – responsible for agreeing which papers will be written, assigning a lead author to each paper, agreeing the co-author list, acting as a guarantor of the paper when the lead author is unable to accept this responsibility, and approving the use of any of the data arising from this study after study has ended and committees cease to exist.

(b) Lead Authors – responsible for deciding who are the co-authors, draft contribution statements and make appropriate acknowledgements, lead the drafting of the publication, circulate drafts for review and enforce deadlines, liaise with SMC or Study Manager about status and organise and requests for funder approval of publications, and act as a guarantor of the paper.

(c) Co-authors – support lead authors in writing and reviewing manuscripts in a timely manner, sign any authorship agreements. Further adjustments or adaptations may be needed for PPI members and the lead author should discuss and agree this with PPI co-authors. Principal investigators may be co-authors if their contribution is justifiable. Reviewing and contributing to a manuscript is mandatory to qualify for co-authorship.

(d) Study Manager – develop, update and maintain publication plan, maintain records of each publication, submit any papers to funder for approval before submission, maintain records of authorship agreements, identify any publication costs in collaboration with the Chief Investigator.

(e) Study Management Group – approves papers for submission, and approves requests for data analysis.

Authorship

(a) A lead author and wider writing team will be established and agreed for each identified paper.

(b) All potential contributors shall have the opportunity to opt into the writing team.

(c) PPI members should be included on relevant publications as authors where appropriate.

(d) It is the responsibility of the Chief Investigator in conjunction with the lead author to decide authorship order in consultation with agreed co-authors. If any disputes arise, the Chief Investigator will take responsibility for reaching a resolution.

(e) All named authors must meet the authorships criteria as detailed within the Authorship Statement below.

(f) Each author must take appropriate public responsibility for the content of publications.

(g) All authors must sign the Authorship agreement (Appendix).

(h) An author is defined as someone who meets the following four criteria based upon the ICJME rules:

   a. Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of the data for the work, and
   b. Drafting the work or revising it critically for important intellectual content, and
   c. Final approval of the version to be published, and
   d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriate investigated and resolved. An author should also be able to identify which co-authors are responsible for specific parts of the work and have confidence in the integrity of the contributions of their co-authors.
   e. Note that special consideration will be given to PPI members who will be contributing in a specialist manner. They must be included appropriately where they have contributed.

(i) Those who have made a contribution but do not fulfil the criteria for authorship will be acknowledged. The lead author of papers will take responsibility for acknowledgements.

(j) All outputs must acknowledge the funder and include any appropriate disclaimer that is required by the funder.

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