Study Protocol

FULL/LONG TITLE OF THE STUDY

NIHR129196 - Adapted suicide safety plans to address self harm, suicidal ideation and suicide behaviours in autistic adults: an interventional single arm feasibility trial and external pilot randomised controlled trial

SHORT STUDY TITLE / ACRONYM

A study of the use of safety plans to reduce self-harm and suicide for autistic adults/ASP

PROTOCOL VERSION NUMBER AND DATE

03, 13th July 2021

RESEARCH REFERENCE NUMBERS

REC Number:	20/WA/0101
SPONSORS Number:	Newcastle University NU-001947
FUNDERS Number:	PHR NIHR129196
Research Registry:	ISRCTN

This protocol has regard for the HRA guidance and order of content.

SIGNATURE PAGE

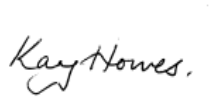
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor

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

For and on behalf of the Study Sponsor:

Signature: Date: 02/06/21



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Joint-sponsor(s)/co-sponsor(s)	NA
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Study Title	Autism Specific Safety Plans to reduce repeat self-harm, suicidal ideation and behaviours in autistic adults: a feasibility trial and pilot RCT
Internal ref. no. (or short title)	Autism Safety Plans
Study Design	1) stage one intervention refinement stage, 2) stage two feasibility study 3) stage three will comprise an external pilot RCT
Study Participants	1) Stage one autistic adults with experience of self-harm, suicidal thoughts or behaviours; family members of autistic people who have experienced self-harm, suicidal thoughts or behaviours; 10 Service providers who support autistic adults. 2) Stage 2 & 3 - autistic adults with experience of self-harm, suicidal thoughts or behaviours; support staff from third sector organisations who support autistic adults.
Planned Size of Sample (if applicable)	Stage one – 10 autistic adults, 10 family members, 10 professionals Stage two – 10 autistic adults, 10 support workers Stage three – 70 autistic adults, up to 35 support workers (some workers may support more than one adult)
Follow up duration (if applicable)	Stage One NA Stage Two – one month Stage three – one month & six months
Planned Study Period	30 months
Research Question/Aim(s)	**Aims and Objectives** The aims of this study are to evaluate the feasibility and acceptability of the use of autism adapted safety plans for autistic adults, and to undertake an external pilot to explore whether the components of a larger future definitive trial are achievable.

	Research Question: Are Autism Specific Safety Plans to reduce repeat self-harm, suicidal thoughts and behaviours acceptable and feasible for use with autistic adults and what are the parameters for a future definitive trial?

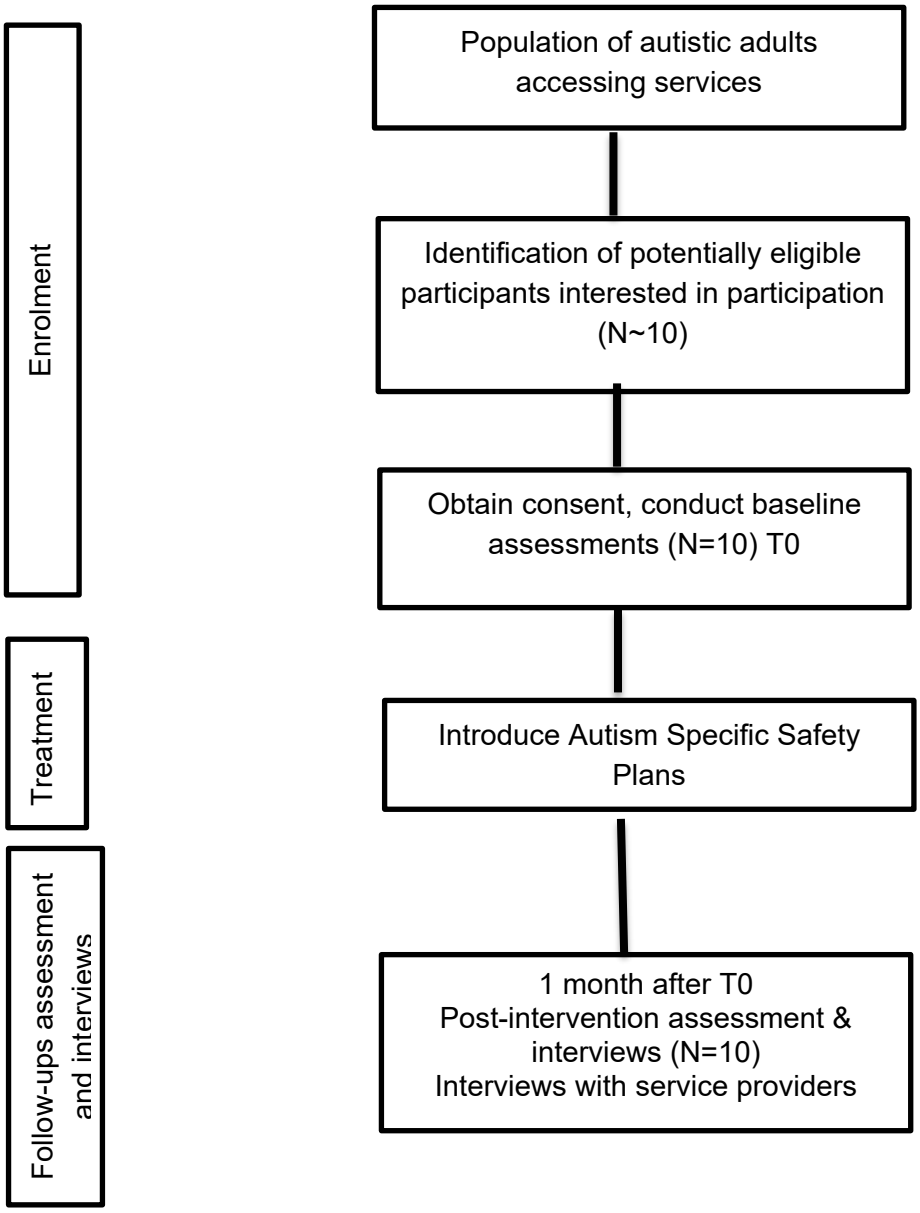
FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
NIHR PHR	NIHR Public Health Research Programme Evaluation, Trials and Studies Coordinating Centre University of Southampton, Alpha House, Enterprise Road, Southampton, SO16 7NS PHR NIHR129196
Autistica	St Saviours House 39-41 Union Street, London, SE1 1SD

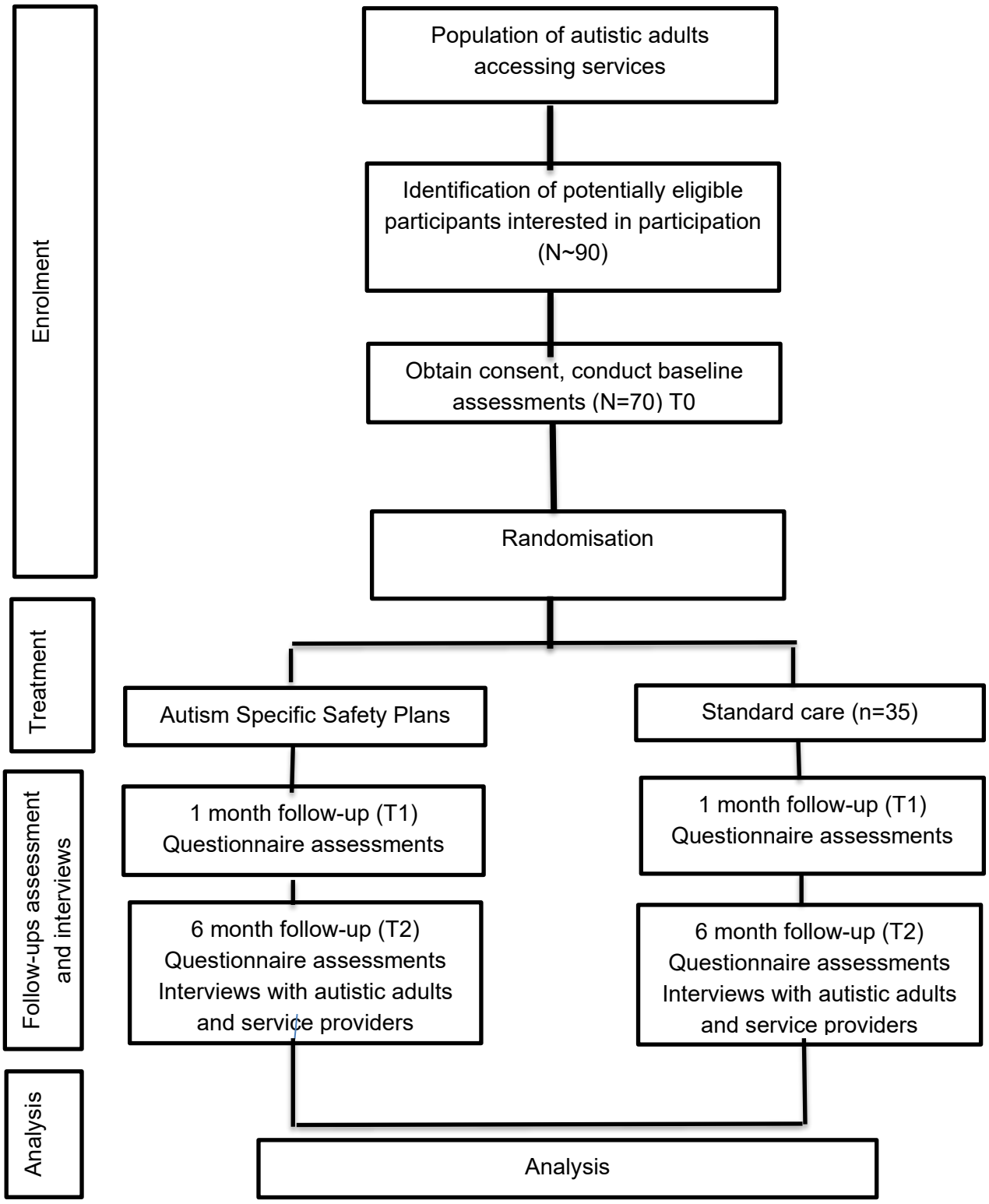
KEY WORDS: Autism, self-harm, suicide, intervention, safety plan, feasibility study, pilot trial

STUDY FLOW CHART

Interventional Single Arm Feasibility Trial CONSORT diagram



External Pilot RCT CONSORT diagram



STUDY PROTOCOL

Autism Specific Safety Plans to reduce repeat self-harm, suicidal ideation and behaviours in autistic adults: a feasibility trial and pilot RCT.

1 BACKGROUND

Suicide prevention is a national priority for UK government policy, and autistic people have recently been identified as a high-risk group in NICE suicide prevention guidelines (NICE 105, 2018). Closing the mortality gap between autistic people and the general population is a priority for the Department of Health's revised "Think Autism Strategy" (2018). Two James Lind Alliance (JLA) priority setting exercises have highlighted as an urgent need research into adapted mental health and suicide prevention interventions for autistic people (Autistica, 2017; Cassidy et al, in prep - INSAR policy brief 2019, see top 10 priorities for suicide prevention research identified in our teams JLA exercise attached).

A systematic literature search was conducted using search terms similar to our previous published review on a similar topic (Cassidy et al, 2018a). The databases PsychINFO, MedLine, Web of Knowledge, and EMBASE were searched using the terms (ASC or ASD or Asperg* or Autis* or high functioning or pervasive developmental disorder* or PDD or HFA) AND (suicid* or "self-harm" or "self-inj*" or parasuicide or "suicide attempts" or "attempted suicide") for articles in the English language published since 1992 (when Asperger's Syndrome was defined as diagnostic category as in current ICD-10 criteria). The search included peer reviewed articles, conference proceedings, theses, and commentaries/opinion pieces, to gauge the direction of the field and work in progress. Also, see attached Cassidy (in press) for a more expansive review of the relevant literature informing this proposal. Additionally, this review is informed by recent published systematic reviews on selection of outcome measures in self-harm research, and RCTs aiming to prevent repetition of self-harm and suicide in autistic and non-autistic samples (Witt et al, 2018; Cassidy et al, 2018a).

Autistic people are a highly disadvantaged group in society, which has been associated with their increased risk of experiencing mental health problems, self-harm, suicidal thoughts and behaviours. In consultation with autistic adults, Griffiths and colleagues (2019) developed a self-report questionnaire, the Vulnerability Experiences Quotient (VEQ), to capture the range and frequency of life disadvantages (across the socio-economic spectrum, including education, employment, finances, social services, criminal justice system contact, and victimisation across the life-course). Autistic adults reported significantly more disadvantages in the VEQ than non-autistic adults, and the VEQ significantly mediated the association between autism diagnosis with depression, anxiety and life satisfaction (Griffiths et al, 2019). This is consistent with previous research showing that high rates of unemployment, unmet healthcare and social support needs in autistic adults are associated with increased risk of self-harm, suicidal thoughts and behaviours in this group (Camm-Crosbie et al. 2018; Cassidy et al. 2018b; Hedley et al, 2017). Ongoing research from our group is also showing that high rates of disadvantage in autistic adults (as measured by the VEQ) are associated with increased risk of suicidal thoughts and behaviours in this group (Pelton et al, under review. See "in press articles" for a copy of the manuscript currently under review). Hence, it is crucial to explore suicide prevention in autism in the context of social

disadvantage. The current proposal will therefore include measures of social disadvantage, consisting of the VEQ in combination with any additional relevant disadvantages identified in partnership with the steering group in stage 1.
Self-harm refers to any self-injury or self-poisoning regardless of suicide intent (Hawton et al. 2012). Self-harm has traditionally been conceptualised very differently in autism compared to the general population, which has led to this behaviour being overlooked by researchers and clinicians. In autistic people, self-harm has been conceptualised primarily as a challenging and/or restricted repetitive behaviour characteristic of autism (Duerden et al., 2012; South et al., 2005) and often associated with co-occurring intellectual disability (ID) (Minshawi et al., 2014). Whereas in the general population, self-harm is conceptualised as a significant risk marker for later suicide attempts (Ribeiro et al., 2015): of those who die by suicide between 50-60% have previously self-harmed (Rodway et al, 2016) furthermore the years of life lost relating to self-harm is 40 years (Bergen et al 2012). A majority (up to 65%) of autistic adults experience self-harm, as conceptualised in the general population (Cassidy et al, 2018b; Maddox et al, 2017), and self-harm is a significant risk marker for suicidal thoughts and behaviours in autistic adults, after controlling for a range of other risk markers (age, gender, unemployment, mental health problems, and satisfaction with living arrangements) (Cassidy et al, 2018b). Autistic people are also significantly more likely to die by self-harm and suicide than the general population (Hwang et al, 2019; Kirby et al, 2019; Hirvikoski et al, 2016). Ongoing work by members of our team analysing coroners' inquest records in the UK also shows that a majority of autistic and non-autistic people who died by suicide had previously self-harmed [Autistica 7249] (Cassidy et al, 2017). Hence, identifying and focusing suicide prevention interventions on people who self-harm, regardless of intent, is crucial for preventing future deaths and a vital element of suicide prevention efforts (Townsend, 2019). Therefore, in the current proposal, repeat self-harm is a primary outcome measure, alongside suicidal thoughts and suicidal behaviours. Autistic adults are the target group for the intervention, given their high risk of dying by self-harm and suicide.

2 RATIONALE

Our research, designed in partnership with autistic adults, highlights a lack of appropriate support and treatment for autistic adults experiencing self-harm, suicidal thoughts and behaviours, as services are not set up for "people like them" (Au-Yeung et al. 2018; Camm-Crosbie et al. 2018). Yet, despite calls for a tailored approach to suicide prevention (Bhugra et al. 2011), no suicide prevention interventions have been developed specifically for autistic people (Hedley & Uljarevic, 2018; Cassidy and Rodgers, 2017). Hence, it is crucial to address this knowledge gap, and develop appropriate interventions to prevent the high rates of self-harm and suicide in autistic people.

A growing body of research is showing that assessments and interventions developed for the general population need to be adapted to meet the unique needs of autistic people. For example, the autism phenotype includes literal interpretation of language, impulsivity, difficulties understanding emotions and reduced flexible thinking and behaviour (APA, 2013), and autistic people present with atypical mental health symptoms (Rodgers et al, 2016; Stewart, 2006). Hence, assessments and

interventions need to be clear, provide support and training for engaging with emotion content, and appropriately capture and address the unique presentation of mental health in autistic people (Cassidy et al. 2018a; 2018c; Cassidy, in press; Wigham et al, 2014; Anderberg et al. 2016; Ghaziuddin et al. 2002).

Our group have identified a potential suicide prevention intervention to adapt in partnership with autistic people and those who support them. At a public engagement event (led by Cassidy), autistic people, their families, practitioners and researchers discussed how we could prevent self-harm and suicide in autistic people. Delegates suggested that suicide safety plans could be potentially very useful to autistic people. An adapted safety plan (SP) was subsequently developed based on this event (see a copy included at the end of this document) and made publicly available. Our adapted SP has been downloaded and shared widely and received positive feedback from the autism community. However, we do not have systematic data on the use of our adapted SPs, which would benefit from further refinement in partnership with autistic people and those who support them. Hence, in the current proposal, we aim to further develop our SPs in partnership with autistic people and those who support them (in stage 1), prior to testing their feasibility and acceptability (in stage 2), and conducting an external pilot RCT with our refined SPs (in stage 3). Our longer-term aim if the proposed pilot RCT was successful, is to subsequently apply to NIHR to conduct a definitive trial testing the effectiveness of our adapted SPs in preventing repeat self-harm, suicidal thoughts and suicidal behaviours in autistic adults.

Safety Plans (SPs) are a simple, scalable and personalisable suicide prevention intervention, with demonstrated effectiveness in a range of clinical groups (Stanley et al. 2018; Green et al. 2017). SPs consist of a prioritized list of hierarchical steps that can be used prior to or during a crisis to mitigate risk of self-harm and suicidal behaviour. SPs involve identification of: (i) Warning Signs; (ii) Internal Coping Strategies; (iii) Social Contacts and Locations; (iv) Family Members or Friends that may offer help or (v) Professionals or Agencies to help; and (vi) How to Keep the Environment Safe. Members of our team have successfully adapted SPs for specific groups, including veterans (O'Connor et al, 2019). SPs are particularly suitable for autistic people due to the concrete steps involved in formulating the plan. Many autistic people do not realise they are approaching a crisis until it is too late, and due to communication difficulties find it difficult to seek help (Camm-Crosbie et al. 2018; Crane et al. 2019). SPs could therefore support autistic people to identify warning signs of approaching crisis, develop personalised strategies, rehearse strategies for seeking help, and restrict access to lethal means. SPs therefore have potential to be effective in reducing autistic peoples' high risk of self-harm and suicide.

3 THEORETICAL FRAMEWORK

Autistic people have significantly higher unmet support needs than non-autistic people (Cassidy et al. 2018b), and experience significant difficulties in accessing NHS clinical services for mental health difficulties (Crane et al. 2019; Camm-Crosbie et al. 2018; AMASE report, 2018). In many regions of the UK, adult autism diagnostic services and post-diagnostic support are delivered by third sector partners and not NHS services. Therefore, a significant proportion of autistic adults experiencing self-

harm, suicidal thoughts and behaviours will not be engaged with NHS services, but rather will be receiving support third sector organisations. In addition, less than one third of people who die by suicide are in contact with clinical services in the 12 months before death (see sites.manchester.ac.uk/ncish/reports/annual-report-2018-england-northern-ireland-scotland-and-wales/). Our partners in the current project include mental health and autism charities who report a crucial need to develop their support for autistic people experiencing self-harm, suicidal thoughts and behaviours. Previous suicide prevention research has also focused on non-NHS services, given that most self-harm occurs in the community and does not present to NHS services, there is a crucial role of third sector services in suicide prevention (Public Health England, 2019; Geulayov et al, 2017). In the case of autism, it will be crucial to develop and explore SPs for use in non-NHS settings, where autistic adults are most likely to receive support.

4 RESEARCH QUESTION/AIM(S)

The aims of this study are to evaluate the feasibility and acceptability of the use of autism adapted safety plans for autistic adults, and to undertake an external pilot to explore whether the components of a larger future definitive trial are achievable.

4.1 Objectives

Stage 1: Intervention Refinement Timescale: Months 0-6.

Objectives: to **refine our autism adapted SPs** in partnership with autistic adults and those who support them. This will ensure that our adapted SPs are suitable for autistic adults (see appendix for a copy of our current template SP developed from a PPI event with autistic adults and those who support them). This intervention refinement stage will be conducted in partnership with relevant stakeholders, including autistic adults, family members of autistic people, and service providers.

Stage 2: Interventional Single Arm Feasibility Trial Timescale: Month 6-10.

Objectives: to conduct an **interventional single arm feasibility trial** to explore data collection tools/methods and gather information to inform the subsequent external pilot RCT in the third and final stage. In stage 2 we will specifically explore:

1. Willingness of service providers to recruit participants;
2. Number of eligible clients within those services;
3. Participant and services views on the proposed research methods and outcome measures;
4. Piloting and further refinement of the bespoke measures to make them fit for purpose.

Stage 3: External Pilot RCT Timescale: Month 10-27.

Objectives: conduct an **external pilot RCT** to gather key data to inform a definitive trial. In stage 3 we will specifically:

1. Record the number of instances of self-harm and suicidal thoughts and behaviours in a six-month period;
2. Explore differences in the primary outcome measure between the intervention and control arm;
3. Record the proportion of autistic participants who utilise the SPs;
4. Record response rates for completion of outcome measures; follow-up rates, response rates to questionnaires/assessments; adherence/compliance rates;

5. Record time needed to collect and analyse data.
6. Obtain participant and service provider feedback on suitability and acceptability of SPs;
7. Investigate potential barriers to and reach of the SPs;
8. Obtain feedback from participants and service providers on methods of recruitment, randomisation and the proposed outcome measures, possible use of reinforcement activities, research procedures and data collection methods to inform a definitive trial;
9. Gather information from participants and service providers on what comprises usual care to inform a definitive trial.

5 STUDY DESIGN, METHODS OF DATA COLLECTION, DATA ANALYIS

5.1 Design

We will undertake a linked study (30 months duration), comprising of three stages: 1) *stage one* will comprise an intervention refinement stage, including consultation with key stakeholders to further refine our adapted SPs (see appendix for a copy of our working draft autism SP developed from a PPI workshop with autistic people and those who support them), and develop our methods, materials and procedures for the study; 2) *stage two* will comprise a feasibility study of the refined intervention, to estimate the important parameters that are needed for the final stage of the work; and 3) *stage three* will comprise an external pilot RCT, to enable us to assess whether the components of a larger study can all work together. It will focus on an evaluation of the suitability of the processes that would be undertaken in a larger definitive study, including recruitment, randomisation, treatment, and follow-up assessments.

5.2 Setting

Autistic adults are typically diagnosed and supported in commissioned non-NHS services, such as social care delivered through local councils, charities and third sector organisations. In addition, less than one third of people who die by suicide are in contact with clinical services in the 12 months before death. Hence, the intervention will be delivered in a number of different settings, including community settings, autism charities and mental health charities. We have agreement from a range of organisations to be partners in the research to facilitate recruitment and deliver the intervention – see letters of support, including national suicide prevention charities (e.g. PAPYRUS, Samaritans), and local support charities (e.g. Harmless, Kayaks, Abel).

5.3 The Intervention

The intervention will be Autism Suicide Safety Plans (SPs), adapted in partnership with autistic people and those who support them, compared to usual care. As described above, SPs consist of a prioritized list of hierarchical steps that can be used prior to or during a crisis to mitigate risk of self-harm and suicidal behaviour. The SP can be personalised to the individual's needs, and have proven efficacy in a range of clinical groups. Our PPI with autistic people and those who support them has identified SPs as a promising intervention to prevent self-harm and suicide in autistic adults. So far, we have developed an adapted SP for autistic adults from our PPI event (see appendix for a copy of this draft SP). The intervention will be delivered by our partners in the non-NHS settings described above (community, autism charities and mental health charities), in addition to the care they usually

provide their clients. In the *stage three* external pilot RCT, we will compare the intervention (autism SPs) in additional to usual care, to usual care only (without the intervention). Please see the sections below for further details of the intervention refinement, feasibility testing, and external pilot RCT.

5.4 Stage 1: Intervention Refinement Timescale: Months 0-6.

Objectives: to **refine our autism adapted SPs** in partnership with autistic adults and those who support them. This will ensure that our adapted SPs are suitable for autistic adults (see appendix for a copy of our current template SP developed from a PPI event with autistic adults and those who support them). This intervention refinement stage will be conducted in partnership with relevant stakeholders, including autistic adults, family members of autistic people, and service providers.

Design: we will convene a series of focus groups to further refine our adapted SPs, and develop our methods, materials and procedures for the study. The focus groups will be run in each of the two separate study sites (Universities of Newcastle and Nottingham). This will allow the research team to identify common themes between the groups and ensure that the adapted SPs are appropriate across the two different sites and slightly different settings where the intervention will be delivered.

Sample: We will recruit 10 individuals (5 in each separate study site), from each of the following groups to participant in Stage One of the study. Our previous experience of similar research has shown that two smaller focus groups of up to 5 is sufficient to reach saturation point, where additional focus groups or larger numbers do not tend to reveal additional new information (e.g. Cassidy et al, 2018b):

A. Autistic adults with experience of self-harm, suicidal thoughts or behaviours;
B. Family members of autistic people who have experienced self-harm, suicidal thoughts or behaviours;
C. Service providers who support autistic adults who have experiences self-harm, suicidal thoughts or behaviours.

Procedure: Three co-production focus groups will take place at each site (Nottingham and Newcastle), facilitated by the site leads (Rodgers and Cassidy) and post-doctoral research assistant. Participants in the focus groups will comprise:

3) 10 autistic adults (5 in each site), aged 18+ years, with experience of self-harm, suicidal thoughts or behaviours; we will work with the Autistica Discover network and with our partner organisations to recruit participants.
4) 10 family members (5 in each site) of autistic people who have experienced self-harm, suicidal thoughts or behaviours; we will work with the Autistica Discover network and with our partner organisations to recruit participants.
5) 10 Service providers (5 in each site) who support autistic adults recruited from our partner organisations.

The co-production focus groups will discuss the following topics:

1. Possible determinants and mediators underlying self-harm and suicidal ideation and behaviours and the use of SPs by autistic people;
2. How our draft SP could be further refined and adapted to better meet the needs of autistic adults;
3. Which sorts of services autistic people use for support with self-harm, suicidal thoughts and suicidal behaviours;
4. Identification of a range of confounders that may impact on findings;
5. Proposed adaptations to the SPs;

6. Acceptability of the proposed study design & materials (including outcomes measures);
7. Acceptability of information and instructions for participants;
8. Barriers and determinants of the use of SPs;
9. How the adapted SPs could be utilised in services and what training would be helpful for service providers;
10. What success or failure of the intervention would look like;
11. What secondary outcomes like impact on quality of life or measures used in the economic evaluation might be measured and the acceptability of alternative methods of measuring these;
12. What the potential adverse outcomes of the SPs might be.

Outcomes from the focus group consultations will include qualitative and descriptive statistics to guide further co-production of the SPs and the methods for stages 2 & 3. We will:

1. Refine our adapted SPs;
2. Agree and potentially adapt an outcome measure to assess self-harm (primary outcome);
3. Consider barriers and facilitators and confounders to using the SPs and identify any features that might indicate drivers of health inequalities that could lead to further refinements;
4. Consider the use of reinforcement activities, determine views on what might be the barriers to using them and what kind of personalised reinforcement strategies might be helpful for autistic adults;
5. Build on and develop and refine our initial logic and dark logic models, whilst refining the intervention;
6. Develop methods to inform a detailed process evaluation to be used in stages 2 & 3;
7. Develop a demographic questionnaire designed specifically for the study to capture information related to potential health inequalities;
8. Develop a Service Use Questionnaire to define treatment as usual for a future definitive trial;
9. Develop tools to measure the costs and effects for the economic evaluation.

Our initial logic model explicitly addresses the underlying determinants and key behaviours to be targeted in the intervention. Based on further input from the consultations we will refine, review and develop our logic model throughout based on emerging findings. The logic model will include specifications of the determinants and mediators underlying self-harm and suicidal ideation and behaviours and the use of SPs by autistic people, including the sorts of services used and the settings and outcomes (positive and negative) of intervention. We will also explore what success or failure of the intervention might look like. This will help refine the conceptual framework and ensure the development of a theoretically grounded intervention and the suitability of outcome measures to capture the range of impacts. We will also assess potential adverse outcomes of interventions in our focus groups (Bonell et al. 2015) and develop a dark logic model. Using the findings from the focus groups and the literature we will identify or develop tools to capture the health and wider benefits of adopting a SP and tools to capture the use of health and social care services (and hence the cost implications of adopting a SP).

Analysis: The intervention refinement stage will enable us to develop SPs that are tailored to the needs of the autism community, gather feedback on important

outcomes and identify training needs for support staff and further refine our logic models. We will analyse these data via descriptive & thematic analysis.

5.5 Stage 2: Interventional Single Arm Feasibility Trial Timescale: Month 6-10.

Objectives: to conduct an **interventional single arm feasibility trial** to explore data collection tools/methods and gather information to inform the subsequent external pilot RCT in the third and final stage. In stage 2 we will specifically explore:

a) Willingness of service providers to recruit participants;
b) Number of eligible clients within those services;
c) Participant and services views on the proposed research methods and outcome measures;
d) Piloting and further refinement of the bespoke measures to make them fit for purpose.

Design: Eligible participants will receive the SP intervention supported by staff in our partner organisations, who will be trained in delivering the SP intervention by the research team. Baseline assessments described below will be collected prior to completing the safety plan with their support work in the partner organisation. One month after completing the safety plan, the participant and their support worker will be asked to complete the follow up assessments described below.

Setting: The intervention will be delivered in our partner organisations, based in non-NHS services (third sector organisations).

Sample: 10 autistic adults who have experienced self-harm, suicidal thoughts or suicidal behaviours will be recruited via our partner organisations. Participants will develop their own SPs with the support of staff in the partner organisation. The primary outcomes are to determine autistic people's views on the refined SPs, explore suitability of outcome measures, trial methods to train staff in the partner organisations, assess fidelity and obtain feedback on whether the SPs need to be refined further before the *stage three* external pilot RCT. Staff from our partner organisations will receive training on using SPs. Staff in our partner organisations will identify clients from their service based on the inclusion criteria (see below).

Inclusion criteria:

As discussed above, adults diagnosed with ASD have been identified as a high-risk group for dying by self-harm and suicide (Hwang et al, 2019; Kirby et al, 2019; Hirvikoski et al, 2016). There is also a strong link between self-harm with suicide attempts and death by suicide in autistic adults (Cassidy et al, 2017; Cassidy et al, 2018b). Hence, the primary outcome measure in the study is repeat self-harm as recommended by a recent systematic review and meta-analysis exploring the most appropriate outcome measure for RCTs aiming to test interventions to prevent self-harm and suicide (Witt et al, 2018). A history of self-harm and/or suicidal thoughts and behaviours in the past 6-months has therefore been recommended as an inclusion criteria for studies exploring psychosocial interventions to prevent repeat self-harm and suicide (according to a previous systematic review and meta-analysis; Hawton et al, 2016). Autistic adults are also likely to be in contact with non-NHS organisations, given the current lack of appropriate and accessible NHS mental health services for this group (Camm-Crosbie et al, 2018; Crane et al, 2019; AMASE report, 2018). Hence, testing our adapted SP intervention for autistic adults is ideal for the NIHR public health call aiming to test the potential of this new intervention to prevent self-harm and suicide in autistic adults in non-NHS services. The SP involves completing a paper form and discussing one’s thoughts and behaviours with

a support worker. Therefore it is important that participants are able to communicate in English in order to engage in the intervention. In light of this evidence and the format of the intervention, the following inclusion criteria will need to be implemented in stages 2 & 3, to ensure that our adapted SPs are utilised in a well-defined group, which is most likely to be able to access and benefit from the intervention:

Inclusion criteria (Stage 2):

1. Adults with a clinical diagnosis of ASD;
2. Accessing services via social care or third sector autism or third sector mental health charities;
3. A self-reported history of self-harm, suicidal thoughts or behaviours within the last 6 months;
4. sufficient spoken English to take part in assessments;
5. Aged 18+ years.

Exclusion criteria (Stage 2)

Insufficient English language skills or literacy to complete the SP and outcome measures (in a future definitive trial we will aim to develop versions of the materials in a range of languages);

Current psychotic symptoms.

Procedure: Stage two of the study is a single arm interventional feasibility study with ten autistic people recruited through social care or third sector partner organisations. At the beginning of stage two support staff from our partner organisations will attend training workshops on the use of adapted SPs, delivered by the research team. Working with our partner organisations autistic adults who meet the inclusion criteria will be identified and invited to participate in this stage of the study. Interested individuals will complete an expression of interest form granting permission for the research associates at each site to make contact with them to provide more information about the study and, where appropriate, obtain informed consent and undertake baseline assessments. We aim to recruit ten autistic people at this stage (5 per site). If more autistic people express interest at this stage, with their permission, we will retain their contact details for stage 3. A trained support worker from the partner organisation that the autistic person was recruited from will be allocated to each participant (wherever possible this will be someone already known to the autistic person). The participant and their support worker will then complete the SP together, the participant can then use the SP as required. With permission we will record the session during which the SP is completed to enable us to determine fidelity. We anticipate that completion of the safety plan will take approximately one hour. The support workers will inform the research associates at each site of the date of completion of the safety plans for each participant. One month after completion of the SPs the research associates will contact the autistic adult and their support worker to complete follow-up assessments, as detailed below. Data consent, data collection and the development of the SP may take place remotely via telephone or video call. The outcomes for stage 2 focus on the feasibility and acceptability of autism adapted SPs delivered via third sector autism or mental health organisations.

Outcome measures for Stage 2:

We will utilise a range of potential outcome measures and seek feedback on their suitability for use in the external pilot RCT (stage 3). We will do this via interviews

with participants and service providers conducted one month after the completion of the SP. The outcome measures detailed below will also be administered at baseline:

1. **A demographic questionnaire** designed specifically for the study to provide information to identify the impact of health inequalities. We will collect information about socio-economic status, employment, housing, access to support, physical health, education, major life events.
2. **Self-harm with and without intent to die** will be assessed by a short form of the Self Injurious Thoughts and Behaviours Interview (SITBI; Nock et al, 2007), in addition to question(s) designed on consultation with the PPI focus groups in *stage one* of the study. The shortened SITBI comprises 74 questions, which we shall reduce further to focus on key information prioritised in partnership with the PPI focus groups in stage one of the study. The SITBI is widely used in research, with acceptable evidence in support of its measurement properties in research.
3. **Mini International NeuroPsychiatric Interview** (Sheehan et al. 1998) will be used to assess psychiatric status of participants, including suicidality. The MINI is a short structured diagnostic interview. It has an administration time of 15 minutes and was designed to meet the need for a short but accurate structured psychiatric interview for clinical trials and as a first step for outcome tracking in clinical services. The MINI is brief and inexpensive, clear and easy to administer, highly sensitive with good specificity and captures current symptomology. As well as providing diagnostic assessment of suicidality and self-harm it provides information relating to anxiety, depression and a range of other psychiatric conditions.
4. **Vulnerability Experience Quotient (VEQ)** (Griffiths et al., 2019) will be used to assess difficult life experiences. The VEQ is a 60-item scale which has been developed through participatory methods with autistic adults to reflect adverse life experiences across 10 themes, such as childhood maltreatment, non-suicidal self-injury, bullying and victimisation as a child or adult and discrimination.
5. **Suicide Behaviours Questionnaire (SBQ-ASC)** (Cassidy et al., 2020) will be used to identify participants' suicidal thoughts and behaviours. The SBQ-ASC was developed through participatory methods with autistic adults. The measure has good content validity, structural validity, internal consistency, convergent and divergent validity, test retest validity, sensitivity and specificity (for distinguishing those with or without lifetime experience of suicide attempt).
6. **EQ-5D-5L** (Herdman et al 2011) is a standardized instrument used as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcomes that reflect the patient's own judgement (also see the economic evaluation section below).

The following measures will be administered at one month follow-up only

7. **System Usability Scale (SUS)** (Brooke, 1996; Bangor et al., 2008). Usability of the SPs for autistic adults will be measured with the SUS. The SUS is a brief, reliable tool for measuring the usability. It consists of a 10 item questionnaire with five response options for respondents; from '*strongly agree to strongly disagree'*. It is

very easy to administer, can be used on small sample sizes with reliable results and can validly differentiate between usable and unusable systems. Administered at one month follow-up only.

8. **Client Satisfaction Questionnaire-8 (CSQ-8)** (Larsen et al., 1979) Acceptability of the intervention will be assessed with the CSQ – 8. This is a brief questionnaire used to assess level of satisfaction with care. It is widely used in mental health settings. Items are scored on a Likert scale from 1 (low satisfaction) to 4 (high satisfaction) with different descriptors for each response point. Total scores range from 8 to 32, with higher scores indicating greater satisfaction. The CSQ-8 has been found to have high internal consistency and concurrent validity in mental health outpatient settings. Administered at one month follow-up.
9. **Time and Travel Questionnaire** designed specifically for the study to provide information to capture travel time, and travel cost related to contacts with health care providers.
10. **Participants Semi-structured Interviews** Interviews with the autistic adults who have participated in stage 2 will be undertaken to gain feedback on the views of the research methods, outcome measures and the SPs.
11. **Professionals Semi-structured Interviews** Staff delivering the SPs will be trained in their delivery and we will assess confidence in delivery and satisfaction with training via semi-structured interviews.

Analysis: Descriptive and thematic data from the interventional single arm acceptability and feasibility trial undertaken in *stage two* will inform the protocol and intervention curriculum for the external pilot RCT and enable us to refine our logic models further. At the end of stage 2 we will have information from both participants and support workers on the acceptability of the outcomes measures, the training of support workers and the use and format of the adapted safety plans and reinforcement activities. Once this data has been gathered it will be summarised by the RAs and presented to all co-applicants and our PPI advisory committee. Modifications to the study materials (including support worker training, SP format etc. will then be agreed by the co-applicant team. The logic model will be also be refined and modified to reflect the emerging findings and PPI input. Based on these findings, methods and measures may be refined for use in Stage three (external pilot).

Progression criteria from Stage 2 to Stage 3:

1. The criterion for recruitment to be met across sites is that at least 60% of autistic participants approached to participant in the feasibility study consent to participate in the study and complete baseline assessments;
2. The criteria for progression to be met are that 10 participants (5 per site) progress from identification/eligibility to participation;

   The criteria for compliance/adherence are that 80% of participants will attend the safety plan session with their support worker, and/or complete the assessments. The criteria for acceptability are that 80% of participants rate the usability of the SPs using the System Usability Scale as 68 or above and that 80% of participants report satisfaction with the SP intervention during the follow up interviews

5.6 Stage 3: External Pilot RCT Timescale: Month 10-27.

Objectives: conduct an **external pilot RCT** to gather key data to inform a definitive trial. In stage 3 we will specifically:

1. Record the number of instances of self-harm and suicidal thoughts and behaviours in a six-month period;
2. Explore differences in the primary outcome measure between the intervention and control arm;
3. Record the proportion of autistic participants who utilise the SPs;
4. Record response rates for completion of outcome measures; follow-up rates, response rates to questionnaires/assessments; adherence/compliance rates;
5. Record time needed to collect and analyse data;
6. Obtain participant and service provider feedback on suitability and acceptability of SPs;
7. Investigate potential barriers to and reach of the SPs;
8. Obtain feedback from participants and service providers on methods of recruitment, randomisation and the proposed outcome measures, possible use of reinforcement activities, research procedures and data collection methods to inform a definitive trial;
9. Gather information from participants and service providers on what comprises usual care to inform a definitive trial.

Design: Eligible participants will randomised to either receive: a) the SP intervention in addition to usual care; OR b) usual care only. The baseline assessments described below will be collected from all participants in both conditions at the start of the study, with follow up assessments one month, and again six months later.
Setting: Non-NHS services (charities, higher education and third sector organisations).
Sample: The external pilot RCT is not powered to estimate a target difference in relative effectiveness, but rather to address outcomes to estimate the parameters for a future definitive trial. For pilot studies, a sample size of around 70 participants at endpoint, randomised to treatment vs. treatment as usual has been recommended to provide sufficient precision to estimate parameters for a full definitive study power calculation (Viechtbauer et al., 2015), therefore 70 participants will be recruited. To account for drop-out, we will recruit 90 participants (45 at each site; Nottingham & Newcastle). Autism is not a rare condition, affecting 1% of the general population, and autistic adults are a high-risk group for suicidal thoughts (up to 66%) and suicidal behaviours (up to 35%). Therefore a majority of autistic adults accessing our recruitment sites will likely be eligible for the study, as confirmed by our partner organisations. We will use the data collected to determine which endpoint is the most suitable for an adequately powered effectiveness trial. A key outcome in trials of the utilisation of SPs is repeat self-harm (see background).

To provide some preliminary consideration of whether a future effectiveness study, following the current study, is potentially deliverable we have performed an exploratory sample size calculation for a future definitive trial. Assuming, based on existing evidence of the rates of self-harm in autism (Cassidy et al, 2018b; Maddox et al, 2017; Cassidy et al. 2014), that up to 66% of the autistic participants in the usual care group will experience repeat self-harm

- Sample sizes of 370 and 500 respectively will provide 80% and 90% power to detect 15% difference in repeat self-harm between the adapted SPs and Usual Care groups.
- Sample sizes of 210 and 280 would have 80% and 90% power to detect a percentage difference of 20% for repeat self-harm.
  These sample size projections are consistent with the guidelines for sample size calculation provided by Arensman et al (2001), which evaluated evidence from general population studies evaluating SPs.
  Given the study population, we expect a clinical consensus of 15% - 20% percentage difference to establish the effectiveness of the adapted SPs. A recent cohort study of safety planning reported 45% fewer suicidal behaviours in the SPs group at six-month follow-up (Stanley et al., 2018). This would indicate that a future definitive trial would be feasible and deliverable with ~550 participants. Given the prevalence of ASD (1% of the general population) and the frequency of self-harm, suicidal thoughts and behaviours within the population this preliminary evaluation of the feasibility of obtaining an adequate sample size for a future definitive trial provide a strong justification for the utility of undertaking the proposed study.
  For the external pilot (Stage 3) we will recruit seventy adults with a confirmed diagnosis of ASD and a self-reported history of self-harm or suicidal ideation or behaviours, via our partner organisations (see letters of support and CONSORT diagram). In a future trial we will aim to develop materials in a variety of languages. We will utilise data from Stage 1 and from service provider interviews to identify which languages it would be useful to translate the SPs to in a future definitive trial.

Inclusion criteria (Stage 3)

1. Adults with a clinical diagnosis of ASD;
2. Accessing services via social care, third sector autism or third sector mental health services or who self -refer into the study;
3. A self-reported history of self-harm, suicidal thoughts or behaviours within the last 6-months;
4. Sufficient spoken English to take part in assessments;
5. Aged 18+ years.

Exclusion criteria (Stage 3)

1. Insufficient English language skills or literacy to complete the SP and outcome measures (in a future definitive trial we will aim to develop versions of the materials in a range of languages);
2. Current psychotic symptoms.

Procedure: Based on data from participants in Stages One (consultation) and Two (pilot feasibility and acceptability trial) and guidance from our partner organisations and the PPI Advisory group, which is comprised of autistic adults, Stage 3 will also include a self-referral route into the study, whereby an autistic person can contact the research team directly should they be interested in participating and if they

consent and are randomised to the active intervention arm they will be paired with a trained support worker or member of the study team to develop their safety plan.

An external pilot randomised controlled trail of the adapted safety plans will be undertaken in stage 3. Recruitment, baseline and outcome assessments for stage 3 take into account modifications suggested by stage 2 findings. At the beginning of stage three we will offer further SP training workshops for support staff from our partner organisations who were not able to participate in training during stage 2. Working with our partner organisations autistic adults who meet the inclusion criteria will be identified and invited to participate. Interested individuals will complete an expression of interest form granting permission for the research associates at each site to make contact with them to provide more information about the study and where appropriate take informed consent and undertake baseline assessments. We aim to recruit 70 autistic people (35 per site) – see sample size calculation above.

After completing baseline assessments participants will be randomised to receive adapted SP+ usual care or usual care. For participants randomised to the Adapted SP+ usual care arm who were recruited via a partner organisation a trained support worker from that organisation will then complete the SP with the participant , the participant can then use the SP as required. Individuals who self-refer will either be linked up with a trained support worker from one of our partner organisations or will complete the safety plan with a member of the research team, based on their preference. In order to ensure blinding of research staff the member of the research team who completes the baseline and follow up assessments with the participant will not complete the safety plan. With permission we will record the session during which the SP is completed to enable us to determine fidelity. Based on data from Stage 2 we anticipate that completion of the safety plan will take approximately one hour. The support workers will inform the research associates at each site of the date of completion of the safety plans for each participant. Data consent, data collection and the development of the SP may take place remotely via telephone or video call.

Follow-up (please also see CONSORT diagram)
Detailed descriptions of these measures can be found under stage 2 above.

Measures for Stage 3 (external pilot):
The following measure will be administered at baseline only, to characterise the mental health profiles of the sample:
Mini International NeuroPsychiatric Interview (Sheehan et al. 1998)

The measures below will be administered at baseline; 1 month & 6 month follow up (primary endpoint):

1. **Self-Injurious Thoughts and Behaviours Interview** (Nock et al, 2007) Primary Outcome
2. **Vulnerability Experience Quotient** (Griffiths et al., 2019)

The following measures will be administered at baseline and 6 month follow-up only:

3. **Demographic questionnaire**

4. **SBQ-ASC** (Cassidy et al., 2021)
5. **EQ-5D-5L** (Herdman et al 2011)
6. **Resource Utilisation Questionnaire** designed specifically for the study to provide information to capture treatment as usual (TAU)/usual care (NHS, local authority and third sector). Participants will complete the measure at baseline for the six months preceding assessment and at six month follow-up for the six months in the trial. This will enable us to obtain detailed information of the use of services for a 12 month period for all participants as well as to undertake a preliminary investigation of the putative differences in TAU between the two treatment arms at follow-up. This is important given a recent review reported that effectiveness of CBT for self-harm varied according to TAU reporting quality and content. Specifically, effects in favour of CBT were found to be strongest in trials in which TAU content was not clearly described (Witt et al., 2018). This is therefore critical information for a future definitive trial, as it will enable us to describe TAU more accurately and estimate likely effect sizes for a clinically meaningful difference between TAU vs, SPs conditions in a future trial.
7. **Time and Travel Questionnaire** designed specifically for the study to provide information to capture travel time, and travel cost related to contacts with health care providers. Participants will complete the measures at baseline for the six months preceding assessment and at six month follow-up for the six months in the trial. This will enable us to obtain detailed information of the use of services for a 12 month period for all participants as well as to undertake a preliminary investigation of the putative differences in TAU between the two treatment arms at follow-up.

   To further inform methods for a definitive study the following measures will be administered at six month follow-up only
   1. **System Usability Scale** (SUS) (Brooke, 1996; Bangor et al., 2008).
   2. **Client Satisfaction Questionnaire-8** (CSQ-8) (Larsen et al., 1979)
   3. **Participants Semi-structured Interviews** Interviews with the autistic adults who have participated in Stage 3 will be undertaken to gain feedback on their views of the research methods, outcome measures and the SPs.
   4. **Professionals Semi-structured Interviews** Interviews with support staff who have participated in Stage 3 will be undertaken to gain feedback on the views of the research methods, outcome measures and the SPs.

To evaluate performance against our progression criteria we will also record:

1. The number of participants who complete the assessments at the primary end point.
2. The percentage of participants who rate the usability of the SPs on the System Usability Scale as 68 or above, at the primary end point.
3. The percentage of participants who report satisfaction with the SP intervention (indicated as a score >20 on the Client Satisfaction Questionnaire-8) at the primary end point.
4. Fidelity of delivery to the SP manual will be undertaken by experts on the delivery of SPs viewing the session with autistic adults during which the SP are developed and rating the session using a bespoke fidelity checklist.

Analysis

In the external pilot RCT the primary and secondary outcomes will be analysed using qualitative and descriptive statistics based on mean, standard deviation, median and interquartile range for continuous data. Number of events and the corresponding percentages will be reported for categorical data. Although no formal sample size calculation was performed, generalised linear models with appropriate distribution for continuous and categorical data will be used to explore associations between the outcomes and other factors including demographic data. In order to identify potential confounder that may be accounted for in a future randomisation scheme for a definitive trial, associations between the outcomes and potential confounders such as service use, family support and loss of benefits will be assessed in multiple regression models. Due to lack of power for an interaction test, a Bayesian model will be used to estimate the posterior probability that an association between an outcome and a confounder is not the same in the SPs intervention and the usual care groups. For example, if the posterior probability is greater 60% we would recommend that such factor is adjusted for in a future definitive trial. The external pilot trial will also provide estimate of missing data, which will calculated as the proportion of participant with outcome data. Using cross-tabulation, we would assess whether participants in the intervention group are more or equally likely report missing outcome data than those in the usual care group. All patients will be analysed under the intention to treat principle, no interim and no sub-group analysis is planned for the external pilot study. Thematic analysis will be conducted on interview data. The logic and dark logic models will be further refined based on the findings at this stage.

Health Economic Evaluation

As the trial will not be adequately powered to conduct a formal economic analysis; the primary objective for the economic component will be to explore aspects of the design of an economic evaluation that will be conducted as part of a definitive RCT. The focus of the economic component will be to determine which form of economic evaluation will be adopted, how resource use and costs will measured and how effectiveness/benefits will also be measured. As noted above a formal economic evaluation will not be performed using data accrued from the pilot trial, rather data will be reported using descriptive statistics. Furthermore, we will look at the distribution of the data points from the pilot trial results to think about candidate statistical distributions that would be suitable for modelling the costs and effects of implementing an autistic specific suicide prevention plan using the results from a definitive trial. The health economist will also look to assess what sort of formal economic evaluation should be conducted for a within-trial analysis should a definitive trial be conducted. We have assumed that by default a cost-consequence analysis (Mauskopf et al., 1998) would be conducted as a minimum for a definitive trial. The cost-consequence analysis involves displaying the costs of the intervention and costs consequent on using the interventions alongside its benefits in a disaggregated manner. The approach simply allows the decision maker to weigh up the costs and consequences and make a decision themselves. An alternative is cost-effectiveness analysis (Drummond et al., 2015). This form of analysis has been used in previous studies that have examined interventions that aim to reduce suicidal

ideation (Spijker et al., 2012). Where costs data would be combined with information on the primary outcome of the definitive trial, with the result presented in the form of the incremental cost per unit change in the primary outcome of the definitive trial. Whilst such an approach will be possible this measure of relative efficiency may be difficult for decision-makers to interpret. Therefore, we will also explore other alternative approaches.

To explore whether cost-benefit analysis (Drummond et al., 2015) would be appropriate we held sought feedback from participants in Stages 1 and undertook discussions with the patient and public advisory group to assess what impacts beyond health could be important (See 'procedure' section above). Based on these data it was determined that cost-benefit analysis could be appropriate therefore we sought to develop a contingent valuation (Drummond et al., 2015)[1] questionnaire for eliciting values of willingness to pay from study participants. We then sought to refine our approach by gathering feedback during stage 2 including discussions with the PPI advisory group. As cost-benefit analysis measures costs and benefits in commensurate units, usually money, we explored whether benefit can be measured in monetary units. Based on these consultations we concluded that the contingent valuation survey would be inappropriate given both the cognitive burden on the trial population, as well as the sensitivity of the subject, to try and elicit a willingness to pay of reduced suicide ideation, or self-harm or try and place a monetary value on a reduction of these outcomes from a societal perspective. For the same reasons the use of more complex methods, such as discrete choice experiments to generate monetary values, were also ruled out.

An alternative to cost-benefit analysis would be cost-utility analysis (Drummond et al., 2015). Cost-utility analysis would typically require health state utilities, likely Health Related Quality of Life (HRQoL) (Drummond et al., 2015) to be collected in order to estimate quality adjusted life years. Standard approaches such as completing the EQ-5D-5L tool at baseline and 6 months will be used to elicit HRQoL values. We will report the completion rates for this tool, responses for each question and health state utility values. However, the EQ-5D-5L might not be sensitive to capture the full impact of adopting the intervention. Therefore, within the focus groups conducted as part of stage 1 we identified likely health effects and explored whether alternative preference elicitation tools such as the standard gamble or time trade-off (Drummond et al., 2015; Torrance et al., 1972) approaches would be more appropriate to capture health state utilities. In doing so, we utilised the team expertise and previous experience of research involving autistic people. However, the sensitivity of the subject and the use of hypothetical mortality probability to generate utilities in standard gamble was deemed inappropriate and complex to use in this context Therefore, only the tools considered appropriate in this study context will proceed to the external pilot in stage 3. All of the methods of economic evaluation would involve assessing the incremental costs of providing an autism specific suicide plan to the trial population as opposed to providing them with usual care. The costs of the intervention will be collected using data collected by a case

report form and a micro-costing exercise. There are also likely to costs consequent on using the interventions. We explored, in the focus group discussions in stage 1 what services are likely to be used; we further refined the list of these services and the resource utilisation/time travel questionnaires after holding discussions with the advisory group and also using our prior experience and previous questionnaires(www.dirum.org). We will report the response rates and completion of each question.

6 ETHICAL AND REGULATORY CONSIDERATIONS

6.1 Assessment and management of risk

The study is a non-CTiMP, pilot interventional, study. Ethical issues in relation to this type of study have been fully considered with ethics committees in relation to extensive previous research by the co-applicant team in studies with similar designs that our research team have previously been involved in. The team are an experienced multi-disciplinary clinical and academic team with considerable experience in developing ethically-minded research procedures specific to autistic people and people experiencing suicidal ideation, behaviours and self-harm. We have developed our assessment schedule to minimise stress and burden. We have considered potential issues related to safeguarding and have built in mitigation of these into the design. All research associates and therapists will be fully trained and have enhanced DBS. A risk register will be developed to manage potential adverse events.

6.2 Safety reporting

For the purposes of this study, only Serious Adverse Events (Adverse Events which meet the criteria for seriousness) will be captured for the participants. Serious Adverse Events will be captured from the start date of the study until the follow-up assessment at Week 24.

6.3 Definitions

Adverse Event (AE): Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the study. Serious Adverse Event (SAE) A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Consists of a congenital anomaly or birth defect
- Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences

* - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Related Serious Adverse Event (RSAE): An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial intervention, based upon the information provided.

6.4 Recording and Reporting SAEs: SAEs must be reported on the study specific SAE report form within 24 hours of a member of the study team becoming aware of the event. For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator

Reporting Exclusions Pre-planned hospitalisations or scheduled procedures for pre-existing conditions do not need to be reported as SAEs, including hospitalisation to give birth.

Recording and Reporting Unexpected Related Serious Adverse Events
There are no related SAEs that are expected for this study and therefore all related SAEs will be classed as unexpected. All unexpected related SAEs occurring from the start date of the study until Week 24 must be reported to the REC. The CI will be responsible for this reporting. Unexpected related SAEs must be reported to the REC no later than 15 calendar days after the CI has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report. As soon as a site suspects that an SAE may be related to the study, they must contact the CI immediately. The reporting timeframe starts at day 0 when the CI is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- Participant number and date of birth
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g. Principal Investigator)

This information must be provided on the trial specific SAE report form.

6.5 Responsibilities
Principal Investigator at each site

- Liaising with RAs to check for SAEs
- Using clinical judgement in assigning seriousness and causality (may be delegated to an alternative clinician).
- Ensuring that all SAEs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

Chief Investigator

- Clinical oversight of the safety of participants, including an ongoing review of the risk/benefit.
- Using clinical judgement in assigning seriousness and causality of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all unexpected related SAEs.
- Review of specific SAEs in accordance with the trial risk assessment and protocol.

Sponsor

- Expedited reporting of unexpected related SAEs to the REC within required timelines (delegated to CI)
- Notification of all investigator sites of any unexpected related SAE that occurs (delegated to CI)

SSC

- Review of safety data collected to date to identify any trends

6.6 Recording and Reporting Events of Special Interest

An event of special interest is any event relating to wellbeing and life difficulties which is not expected and not anticipated in 'normal day-to-day life', but is not a physical medical event. Events of special interest will be recorded for participants from the start date of the study until the follow-up assessment at Week 24.

Examples of events of special interest may include:

1. Participant no longer attending work/college (or other form of education)
2. Relationship breakdown
3. Housing/financial changes
4. Decline in family/partner mental health sufficient that help sought from GP/medical practitioner
5. Other significant family issues/ breakdown/ bereavement

This list is not exhaustive and other events of special interest should also be reported at the discretion of the investigator. RAs who become aware of events of special interest should inform the site PI, who will record all events of special interest at site.

For each event of special interest, the following will be recorded:

- Participant number
- Date of notification of the event
- Stage of study
- Description of the event

Events of special interest will be collected from sites after each stage and at the end of the study and reviewed by a TMG sub-committee, as well as the SSC.

6.7 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a study against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the sponsor must be notified immediately and details of the USM given. The CI must

inform the REC within 3 days of the USM taking place in accordance with the NCTU's standard operating procedures.

6.8 Research Ethics Committee (REC) and other Regulatory review & reports

A favourable ethical opinion was been obtained for Stages 1&2 via IRAS (REC 20/WA/0101) on 19th May 2020.A favourable ethical opinion was obtained for Stage 3 following completion of Stage 2 and confirmation of the outcome measures for Stage 3 on 12th July 2021. All parties will conduct the trial in accordance with this ethical opinion. The CI will notify the NU REC of all required substantial amendments to the study and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The CI will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or USARs that occur during the study. The CI will notify the REC of the early termination or end of study in accordance with the required timelines.

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Management Group & Study Steering Committee. Substantial amendments will be submitted to the REC and will not be implemented until this approval is in place. Non-substantial amendments may be made at any time with a record of the amendment held in the Trial Master File. Any non-substantial amendment that requires an update to the trial documentation will be submitted to the REC for acknowledgement of the revised version of the document. Informed consent will be obtained from participants by the trained research associates. We have developed our assessment schedule to minimise stress and burden. We have considered potential issues related to safeguarding and have built in mitigation of these into the design. All research associates and therapists will be fully trained and have enhanced DBS.

6.9 Peer review

The trial has undergone peer review as arranged by the NIHR PHR programme as part of the funding process. The protocol has been reviewed and authorised by the sponsor, funder, Chief Investigator and co-applicants.

6.10 Patient & Public Involvement

PPI is embedded throughout the proposed study. A funded member of the co-applicant team is an autistic person with a wealth of research experience and an academic background in public health. As a member of the research team they will be a member of the steering committee and will advise on ethical issues, participant facing documentation, interpretation of findings and dissemination. In addition we will create a PPI advisory committee which will meet regularly (see Gantt chart) and will be comprised of autistic adults with lived experience of the mental health difficulties, including self-harm and suicidal thoughts and behaviours. We will work closely with existing autism community networks and through the Autistica led Discover network to ensure that our advisory committee is as representative of the community as possible. We aim to recruit around ten members to the committee on the assumption that not all member will be able to attend each meeting. We will encourage members

of the advisory committee to participate in Autistica led training on involvement if they have not already accessed this. We will convene regular meetings of the committee (see Gantt chart) and welcome participation using a variety of different methods to suit individual needs, circumstances and preferences (including face to face attendance, skype/conference call participation and submission of written feedback). The advisory committee will provide guidance and feedback at all stages of the study including recruitment strategies, documentation, methods, interpretation and dissemination of findings. Participants will be re-numerated for their time at INVOLVE rates and reimbursed for any out of pocket expenses. Additionally members of the autism community will be involved in the research as research participants at all stages and through this mechanism will feedback on the research materials and design. During Stage One autistic adults, family members and professionals will participate in focus groups specifically designed to garner advice, guidance and feedback on the study. The opportunity to provide views on the materials and methods used is also embedded in stages 2 & 3 in the form of semi structured interviews regarding the study design, methods and outcome measures. It is through the extensive use of PPI embedded in every aspect of the study that we will gain crucial feedback to inform the design and methods for a future definitive trial.

6.12 Protocol compliance

It is the responsibility of the CI to ensure that the study is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI will retain overall responsibility. Protocol deviations, non-compliances or breaches are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events will be documented and reported to the Sponsor in accordance with SOPs. Deviations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach.

6.13 Data protection and patient confidentiality

Data will be handled, computerised and stored in accordance with the General Data Protection Regulation.

6.14 Indemnity

The sponsor (Newcastle University) will provide indemnity in the event that participants suffer negligent harm due to the management of the study. This indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial. The trial sites will provide indemnity in the event that participants suffer negligent harm due to the conduct of the study at their site. This is a non-commercial study and there are no arrangements for non-negligent compensation.

6.15 Data Handling and Record Keeping

Overall responsibility for data collection lies with the CI. Data collected on paper assessment tools will be entered onto a secure validated data management system at sites. A unique trial number is allocated at recruitment and will be used to identify participants on all paper data collection forms throughout the duration of the study. No participant identifiable data will leave the study sites. The quality and retention of study data will be the responsibility of the CI. All study data will be retained in accordance with the latest directive on GCP (2005/28/EC) and local policy.

6.16 Access to Data

Staff involved in the conduct of the study, including the PIs, Trial Management Group and RAs will have access to the site files. Clinical information shall not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities or the REC. Secure anonymised electronic data may however be released to the trial statistician for analysis. The PI and site staff involved may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. The data will be the property of the Chief Investigator and Co-Investigators. Any requests to access the final trial dataset may be considered under the NU data sharing policy.

7 DISSEMINATION POLICY

7.1 Dissemination policy

The dissemination strategy for the study has been designed in partnership with autistic adults. The strategy includes several complementary strands of activity:

1. Newsletters summarising the progress and findings will be designed by the research team and autistic advisors and sent to participants and services who have taken part in recruitment, during the study to support retention, and at the end to share findings.
2. A dissemination event to be held at the end of the study at each site, the findings of the study will be presented to autistic adults, local professionals, the study steering group and stakeholders who supported the study.
3. The findings will be disseminated to social care providers, including Crisis Resolution and Home Treatment Teams.
4. Dissemination will take place to mental health charities, such as the Samaritans and the Mental Health Foundation and Mental Health Matters as well as autism charities such as the National Autistic Society, Autistica, Kayaks, Autism in Mind through presentations, websites, newsletters and training.
5. The autistic members of the steering group, with support from the research team, will submit an article to the INVOLVE newsletter and present the study findings at appropriate third sector/professional conferences e.g. National Autistic Society Annual Conference. Reports in accessible newsletters such as Your Autism and Your Impact (NAS), Asperger United will also be prepared.
6. Dissemination via websites (partner & University) & social media to access a wider audience.
7. The study protocol will be published and findings written for academic peer reviewed journals (including open access) and presented at relevant conferences.
8. Workshops will be held for autistic adults, clinicians, service managers and commissioners to discuss the implications of the research.

9. The study findings will be disseminated to the national suicide presentation strategy steering group for inclusion into future progress reports.

Authorship eligibility guidelines and any intended use of professional writers
Authorship eligibility will be determined in line with an agreed dissemination plan and will comply with ICMJE guidelines. We will not use professional writers.

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9. APPENDICES

Appendix A

Schedule of Events: Stage 1 Consultation

Procedure	Screening	Focus Group
Information Sheet	X	
Informed Consent	X	
Eligibility	X	
Questionnaires & safety plans for comment		X
Debrief Sheet		x

Schedule of Events: Stage 2 Feasibility Study

Procedure	Screening	Baseline	1 Month Follow-up
Autistic adults & professionals			
Information Sheet	X		
Informed Consent	X		
Eligibility	X		
Autistic adults only			
Demographics*		X	
SITBI		X	
MINI		X	
VEQ		X	
SUS			X
CSQ-8			X
Semi-Structured Interviews			X
Professionals only			
Professionals Semi-Structured Interviews			X
Autistic adults & professionals			
Debrief Sheet			X

*Demographics to include – Socio-economic status, employment, housing, access to support, physical health, education, major life events.

Schedule of Events: Stage 3 External pilot

Procedure	Screening	Baseline	1 Month Follow-up	6 Month Follow-up
Autistic adults & professionals				
Information Sheet	X			
Informed Consent	X			
Eligibility	X			
Autistic Adults Only				
Demographics*		X	X	X
SITBI		X	X	X
MINI		X		
VEQ		X	X	X
EQ-5D-5L		X	X	X
Resource Utilisation		X	X	X
Time and Travel Questionnaire		x	x	x
Randomisation**		X		
SUS				X
CSQ-8				X
Participants Semi-Structured Interviews				X
Professionals Only				
Professionals Semi-Structured Interviews				X
Autistic adults & professionals				
Debrief Sheet				X

*Demographics to include – Socio-economic status, employment, housing, access to support, physical health, education, major life events.
**Randomisation to take place following completion of baseline assessment.

Protocol Version	Date	Changes	Notes
1	3rd March 2020	NA	
2	7th December 2020	a) Introduce remote/virtual consent and assessment procedures	To address COVID restrictions
3	3rd May 2021	a) Confirm outcome measures for Stage 3 b) Introduce self referral route to Stage 3 c) Replace Prof Kasim with Dr Ogundimu	

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