FULL TITLE: The Prevalence of **S**ocial Communication **PR**oblems in Adult Psychiatric **IN**pa**T**ients (The **SPRINT** study)

SHORT TITLE: The SPRINT Study

PROTOCOL VERSION: 1.1

DATE: 14/02/2019

SPONSOR: University of Leicester

IRAS NUMBER: 235424

SPONSORS NUMBER: 0684

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1. DETAILS PERTINENT TO STUDY

1.1. 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:

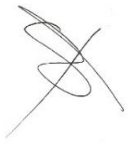
Signature:

Name:

Position:

Date:

Chief Investigator:

Signature: 

Name: Sam Tromans

Date: 14/02/2019

1.2. Key Study Contacts

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1.3. Study Summary:

Study Title:	The Prevalence of **S**ocial Communication

	PRoblems in Adult Psychiatric **IN**pa**T**ients (The **SPRINT** study)
Short title:	The SPRINT Study
Study design:	Cross-sectional study
Study participants:	Males and females aged between 18-65 years on the date of their most recent psychiatric hospital admission. English speaking. Absence of a clinical diagnosis of dementia.
Planned size of sample:	Phase 1: 200 participants Phase 2: 40 participants
Planned study period:	1st November 2018 – 1st June 2021
Aims:	• To estimate the prevalence of Autism Spectrum Disorders (ASD's) amongst adults who have been admitted to psychiatric hospitals (including those with intellectual disabilities) population of adult psychiatric inpatients. • To examine the association between other mental and physical health conditions in adults who meet diagnostic criteria for ASD's with those who do not meet such criteria (all of whom have been admitted to a psychiatric hospital).

1.4. Funding and Support in Kind:

Funder	Financial and non-financial support given
Leicestershire Partnership NHS Trust	Funding for the chief and principal investigators salary. Support with study development.
University of Leicester	Provision of workspace for the chief and principal investigator. Support with study development. Financial support (provided from research group).

1.5. Role of Sponsor

The sponsor (University of Leicester) is involved in conducting an initial sponsor review, involving comprehensive assessment of the proposed research study and related documentation. Additionally, the sponsor takes legal responsibility for the overall conduct of the research.

1.6. Roles and Responsibilities of Study Management Committees and Individuals:

The research plan for this study has been refined following consultations with patients, carers and representatives. This has initially taken place in the form of two discussions of the proposed study with groups of mental health service users. One discussion was with patients with intellectual disabilities (ID) and their carers, and the second involved patients without ID and their carers.

Additionally, there will be patient and carer representation on the steering group, including: 1) At least two people with ASD's (including at least one person with comorbid ID), and 2) At least two professional carers or family members for people with an ASD (including at least

one person whom has cared for a patient with an ASD who has previously been an inpatient in a psychiatric hospital). We also plan to actively involve people with ASD's and their carers in the development of dissemination materials pertaining to the study's findings.

The Clinical Research Group in Forensic Intellectual and Developmental Disabilities (CRG-FIDD) website (2018) will have a plain English summary of the study. Additionally, the study will be discussed with the National Professional Advisor for Learning Disabilities at the Care Quality Commission.

1.7. Protocol Contributors:

The study protocol was designed by Dr Sam Tromans, Professor Terry Brugha, Dr Reza Kiani, Dr Regi Alexander and Professor Mohammed Al-Uzri. The sponsor (University of Leicester) was consulted with regard to the study design, as part of their review process prior to providing sponsorship authorisation.

Patients and carers have been consulted in the process of developing the study protocol. Their involvement has led to several changes to the study design, including:

- Providing the option for participants to have a brief summary of their Phase 2 diagnostic assessment forwarded to their Consultant Psychiatrist and/or General Practitioner
- The inclusion of the Stigma Questionnaire for people with Intellectual Disability (SQID) for participants whom have an ID.
- Shortening of the Diagnostic Interview for Social and Communication Disorders (DISCO) interview to the algorithm questions, psychiatric conditions section and

forensic problems section only (DISCO-A), rather than conducting the interview in its full form

1.8. Keywords:

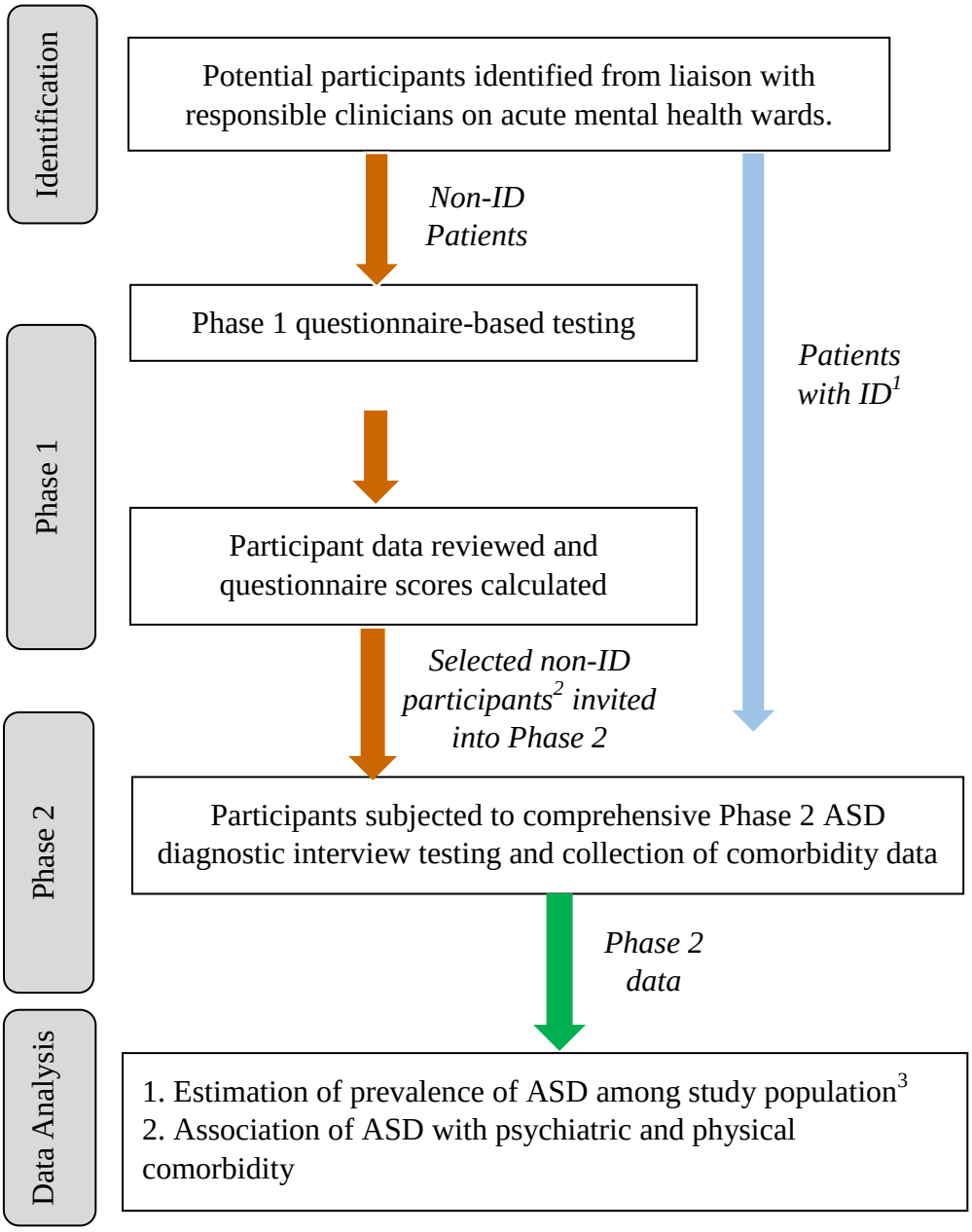
Autism spectrum disorder, Social communication disorder, Psychiatric inpatient, Intellectual disability, Prevalence, Comorbidity

1.9. Study Flow Chart:

[1]Participants with ID will bypass Phase 1 questionnaire-based testing, and progress to Phase 2.

[2]Probability of Phase 2 selection determined by scores on the AQ, with probability increasing with increasing scores (and thus increased predicted probability of ASD).

[3]Prevalence estimate will be adjusted for selection and non-response.



Timetable:

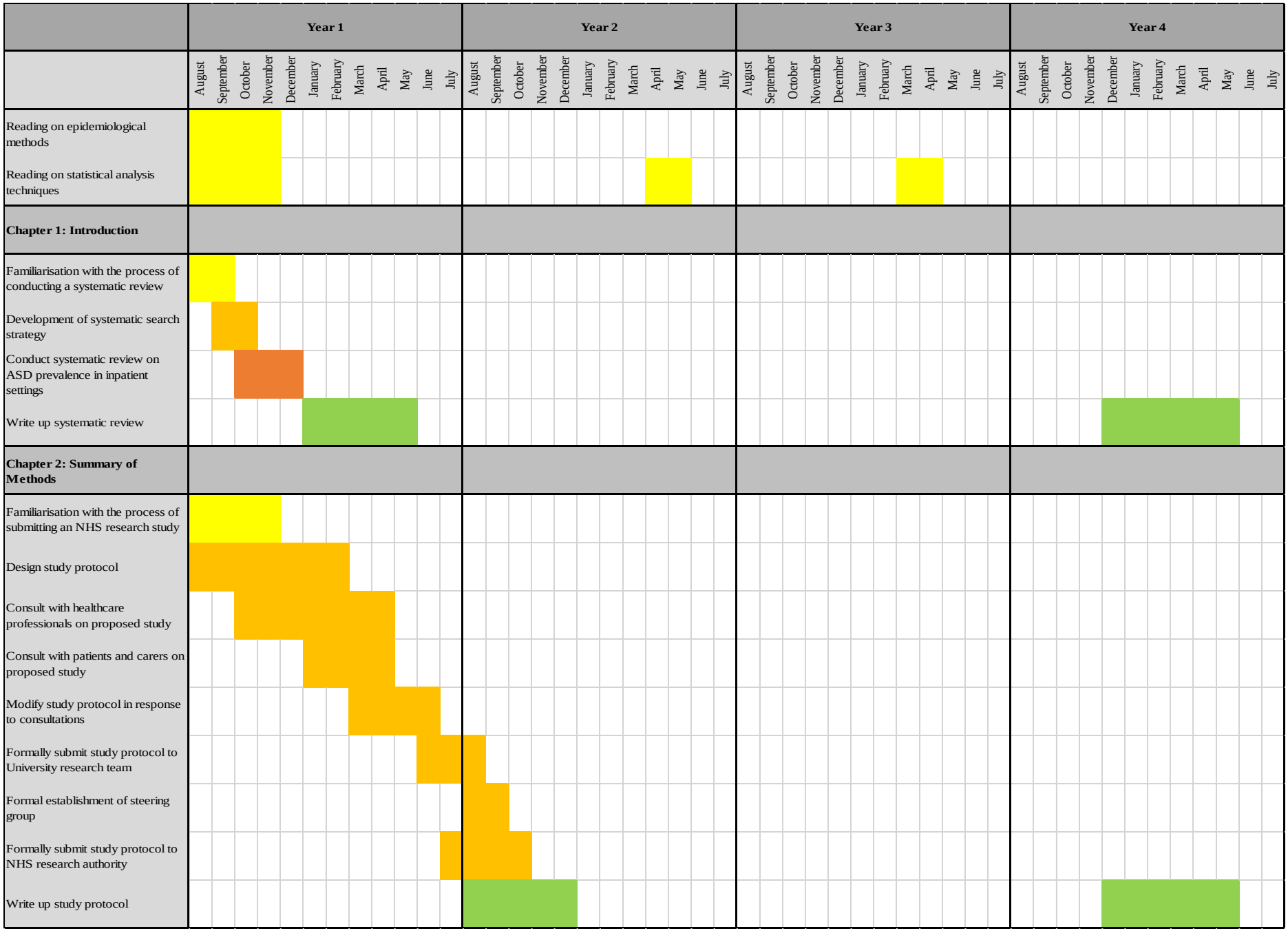
With regard to the proposed timescale of the project, the full study is intended to be completed and thesis submitted within 4 years of commencement. Please refer to Table 1 for an overview of the project timeline. During the data collection period, we will be collecting

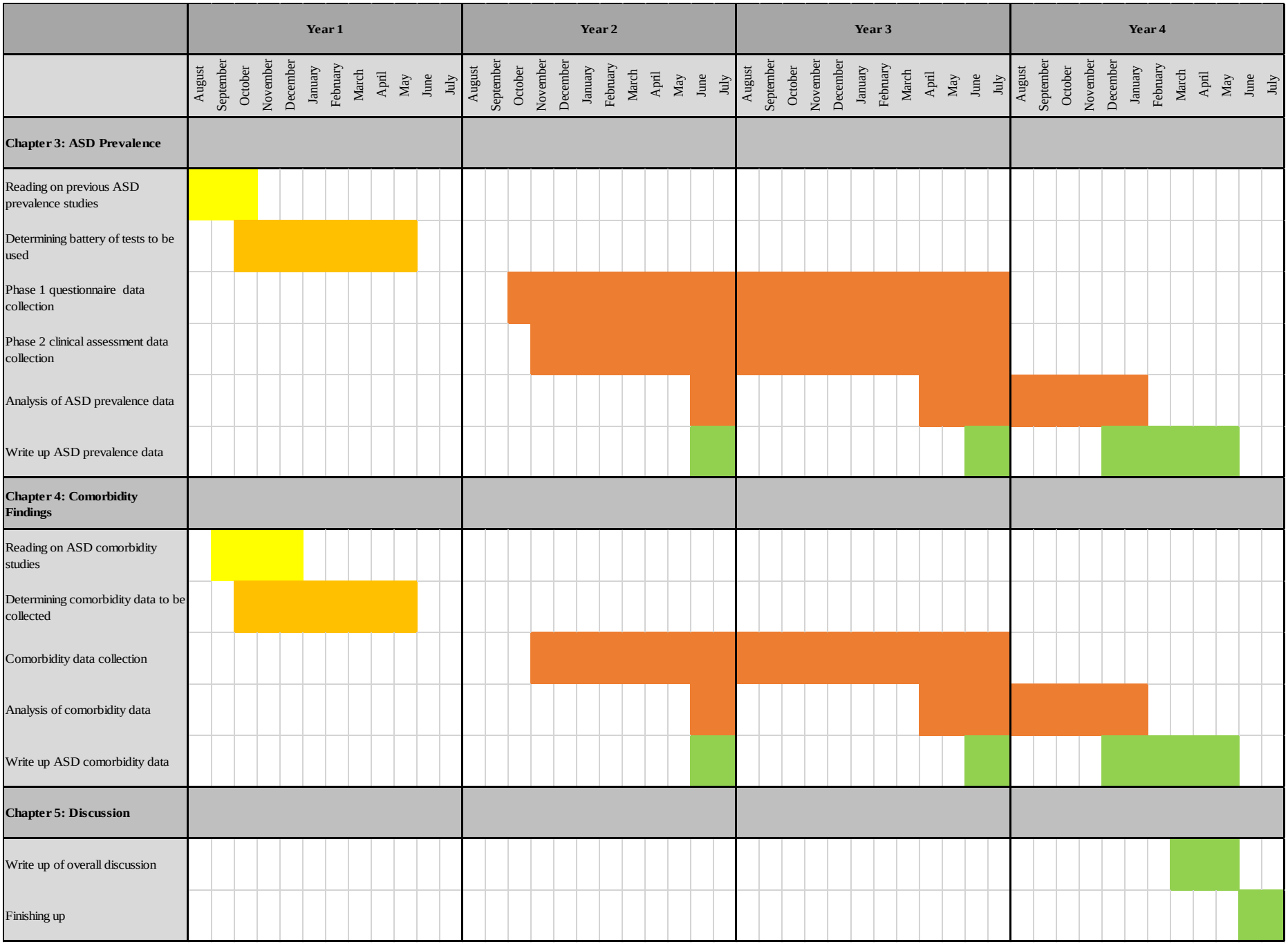
Phase 1 data for an average of 5 participants per week, and Phase 2 data for an average of 1 participant per week.

Table 1: Gantt chart, illustrating the project timeline.

Key:

Task subtype	Corresponding Colour
Reading/familiarisation	
Method development	
Method implementation	
Writing up	


Year 1
Year 2
Year 3
Year 4
August
September
October
November
December
January
February
March
April
May
June
July
Reading on epidemiological methods
Reading on statistical analysis techniques
Chapter 1: Introduction
Familiarisation with the process of conducting a systematic review
Development of systematic search strategy
Conduct systematic review on ASD prevalence in inpatient settings
Write up systematic review
Chapter 2: Summary of Methods
Familiarisation with the process of submitting an NHS research study
Design study protocol
Consult with healthcare professionals on proposed study
Consult with patients and carers on proposed study
Modify study protocol in response to consultations
Formally submit study protocol to University research team
Formal establishment of steering group
Formally submit study protocol to NHS research authority
Write up study protocol


Year 1
Year 2
Year 3
Year 4
August
September
October
November
December
January
February
March
April
May
June
July
Chapter 3: ASD Prevalence
Reading on previous ASD prevalence studies
Determining battery of tests to be used
Phase 1 questionnaire data collection
Phase 2 clinical assessment data collection
Analysis of ASD prevalence data
Write up ASD prevalence data
Chapter 4: Comorbidity Findings
Reading on ASD comorbidity studies
Determining comorbidity data to be collected
Comorbidity data collection
Analysis of comorbidity data
Write up ASD comorbidity data
Chapter 5: Discussion
Write up of overall discussion
Finishing up

2. STUDY PROTOCOL:

The Prevalence of Social Communication PRoblems in Adult Psychiatric INpaTients (The SPRINT study)

2.1. Plain English Abstract:

Problems with Social Communication (PSC), including Autism Spectrum Disorders (ASD's), are lifelong and associated with difficulties in social interaction, communication and restricted, repetitive behaviours. Most research has focused on these issues in childhood. Little is known about how common ASD's and other PSC are among adults, including those admitted to psychiatric hospitals.

Identifying people with ASD's and other PSC will enable them to access services appropriate for their needs that can improve their quality of life. There is a risk that these people are otherwise incorrectly diagnosed with other mental disorders, and offered treatments unlikely to be helpful for them. Nevertheless, some people have both PSC or ASD and other mental and physical health conditions (comorbidities), though the extent of this problem is poorly understood.

This study aims to:

- (1) Estimate how common ASD's are amongst adults who have been admitted to psychiatric hospitals (including those with intellectual disabilities).
- (2) Examine the association between other mental and physical health conditions in people who meet diagnostic criteria for ASD with those who do not meet such criteria (all of whom have been admitted to a psychiatric hospital).

We will collect data on patient's ASD test scores (on measures designed to identify possible ASD's and PSC) and physical and mental health (Phase 1). Tests will include the Autism Quotient (AQ), the informant version of the Social Responsiveness Scale, 2nd edition – Adult (SRS-2), the Adult Social Behaviour Questionnaire, (ASBQ, both the self and informant versions) and the EuroQol-5D-5L (EQ-5D-5L). A subgroup of patients, selected via stratified random sampling according to AQ score, will be invited into Phase 2, involving comprehensive ASD diagnostic criteria testing (Autism Diagnostic Observation Schedule, ADOS-2), a measure of childhood delay in social and communication development (the diagnostic algorithm, psychiatric conditions and forensic problems items within the Diagnostic Interview for Social and Communication Disorders, DISCO-A) and the ASD interview within the Schedules for Clinical Assessment in Neuropsychiatry version 3 (ASD-SCAN-3). Patients with intellectual disabilities will bypass Phase 1 ASD tests, progressing directly to Phase 2, as well as not undertaking ASD-SCAN-3 testing, though they will be instead tested with the Stigma Questionnaire for people with Intellectual Disability (SQID). All Phase 2 patients will be given a standardized interview regarding their basic information, as well as interviewed on the Physical Health Conditions and Mental Illness Diagnoses and Treatment sections of the 2014 Adult Psychiatric Morbidity Survey (APMS). Following the Phase 2 interview process, checklists for internationally recognised diagnostic criteria for ASD (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems Diagnostic Criteria for Research [ICD-10-DCR] and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5]) will be completed by the assessing member of the research team, to establish whether the patient satisfies such criteria.

The study's findings aim to improve our understanding of both the prevalence of ASD among adults admitted to psychiatric hospitals, and the healthcare needs of this group. This will

directly benefit patients with ASD, via enabling us to design inpatient services better suited to identifying them in a psychiatric hospital setting and meeting their healthcare needs.

2.2. Scientific Abstract:

Background:

People with Autism Spectrum Disorders (ASD's) often have delayed diagnoses, or remain undiagnosed throughout their adult life. Though ASD's are associated with multiple comorbid psychiatric diagnoses, most epidemiological studies have principally focussed on their prevalence in the community, rather than the adult psychiatric inpatient setting, where there is a comparatively limited evidence base.

Aims:

This study aims to estimate the prevalence of ASD's amongst adults who have been admitted to psychiatric hospitals, including those with intellectual disabilities (ID). Additionally, we aim to examine the association between other psychiatric and physical conditions in adults who meet the diagnostic criteria for ASD's with those who do not meet such criteria (all of whom have been admitted to a psychiatric hospital).

Methods:

Adult inpatients from two acute mental health inpatient units within Leicestershire (Bradgate Mental Health Unit and the Agnes Unit) will form the study population. Inclusion criteria for the study include being >18 and < 65 years of age on the date of their admission and being (or having been) a psychiatric inpatient. Exclusion criteria include patients under the age of 18 years or over the age of 65 years on the date of their admission, not understanding verbal and/or written English, having a clinical diagnosis of dementia and/or having no history of

being a psychiatric inpatient. Additionally, patients lacking capacity will be excluded if they become distressed by the assessment process (at any point) or if their guardians are not in agreement with them remaining in the study.

The study will utilise a multiple phase design, where Phase 1 will entail initial testing of approximately 200 patients, using the Autism Quotient (AQ), the informant version of the Social Responsiveness Scale, 2nd edition – Adult (SRS-2), the Adult Social Behaviour Questionnaire (ASBQ, both the self and informant versions) and the EuroQol-5D-5L[1] (EQ-5D-5L). Patients with ID will bypass ASD testing in Phase 1, progressing directly to Phase 2.

Phase 2 will involve a subgroup of 40 of these patients undergoing comprehensive diagnostic criteria testing with the diagnostic algorithm, psychiatric conditions and forensic problems items for the Diagnostic Interview for Social and Communication Disorders (DISCO-A), the Autism Diagnostic Observation Schedule version 2 (ADOS-2) instrument and the ASD interview within the Schedules for Clinical Assessment in Neuropsychiatry version 3 (ASD-SCAN-3)[2]. Of this patient subgroup, 25 (±5) patients will not have ID, and will be selected via stratified random sampling according to AQ questionnaire score, and 15 (±5) patients will have ID, and will progress directly to Phase 2. Patients with ID will not undergo ASD-SCAN-3 testing, but will instead be tested with the Stigma Questionnaire for people with Intellectual Disability (SQID). All Phase 2 patients will be given a standardized interview regarding their basic information, as well as interviewed on the Physical Health Conditions and Mental Illness Diagnoses and Treatment sections of the 2014 Adult Psychiatric Morbidity Survey (APMS). The sequence in which the Phase 2 interviews are administered will be random, to address any bias associated with interview order. Following the Phase 2 interview process, checklists for internationally recognised diagnostic criteria for ASD (the

[1] Completed by both patient and informants, to describe their own respective general health states.
[2] Patients with ID will not undergo ASD-SCAN-3 testing, as it has not been developed for intended use in this patient group.

10th revision of the International Statistical Classification of Diseases and Related Health Problems Diagnostic Criteria for Research [ICD-10-DCR] and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5]) will be completed by the assessing member of the research team, to establish whether the patient satisfies such criteria.

Such a multi-phase approach enables coverage of a larger patient population (Elsabbagh et al., 2012), and has been previously utilised in epidemiological research into ASD prevalence in both child (Baird et al., 2006; Kim et al., 2011) and adult populations (Brugha et al., 2012; Scragg & Shah, 1994). Basic information pertaining to demographic details and previous inpatient psychiatric admissions will also be collected from all participants in both phases.

Potential Benefits to Patients:

Individuals who participate in this study cannot be assured that they will directly benefit from the research themselves. However, the findings of this study will add to the currently limited evidence base in terms of the prevalence of ASD among adults admitted to psychiatric hospitals, and the healthcare needs of this group. This will hopefully benefit future patients with ASD, via helping in securing appropriate allocation of resources by healthcare providers as well as designing inpatient services better suited to the needs of this group.

2.3. Background and Rationale:

Autism Spectrum Disorders (ASD's) are lifelong neurodevelopmental conditions characterised by impairments in reciprocal social interaction and communication, as well as restricted, stereotyped and repetitive behaviours (World Health Organization, 1992). They represent a major global public health issue, responsible for over 111 Disability Adjusted Life Years (DALY's) per 100,000 persons (Baxter et al., 2015). Community-based prevalence

rates for ASD's in the general population show considerable variation across studies, though recent systematic reviews and large-scale epidemiological research estimate rates of between 0.7-1.1% (Baxter et al., 2015; Brugha et al., 2016).

Whilst there has been limited research into the prevalence of ASD's within an adult psychiatric inpatient setting (Tromans, Chester, Kiani, Alexander, & Brugha, 2018), previous work suggests that it could be significantly greater than that of the general population and that they may be substantially underdiagnosed in this group, with prevalence estimates varying from 1.5 – 9.9% (Hare, Gould, Mills, & Wing, 1999; Mandell et al., 2012; Scragg & Shah, 1994; Shah, Holmes, & Wing, 1982). For further information pertaining to these previous prevalence studies, please refer to Appendix One. Suggested reasons for such under diagnosis, if shown to be valid, include many adult psychiatrists lacking training in disorders first originating in childhood, failure to take a comprehensive developmental history, and misdiagnosis for other forms of mental disorder (Konstantareas & Hewitt, 2001; Mandell et al., 2012). Additionally, presence of comorbid psychiatric disorders that are more common in people with ASD's could potentially complicate the diagnostic picture (Billstedt, 2000), including depression (Ghaziuddin, Ghaziuddin, & Greden, 2002; Hofvander et al., 2009; Rai et al., 2018), bipolar disorder (Croen et al., 2015), anxiety disorders (Mazzone, Ruta, & Reale, 2012), schizophrenia (Croen et al., 2015), attention deficit hyperactivity disorder (Hofvander et al., 2009; Mazzone et al., 2012), alcohol and substance abuse (Croen et al., 2015), as well as ID (Emerson & Baines, 2010; Strømme & Diseth, 2000).

Current evidence suggests that children with ASD's are at greater risk of a range of comorbid physical illness compared to their non-ASD peers, including obesity (Eaves & Ho, 2008; Granich et al., 2016; Ho, Eaves, & Peabody, 1997), epilepsy (Levy et al., 2010; Schieve et al., 2012), asthma (Schieve et al., 2012), sleep disorders (Bauman, 2010) and gastrointestinal disorders (Bauman, 2010). In contrast, relatively little is known about the burden of physical

comorbidity among adults with ASD's (Croen et al., 2015; Rydzewska et al., 2018), though from the evidence available, the aforementioned conditions appear to persist into adulthood (Croen et al., 2015; Kohane et al., 2012).

Stigma, defined as a "phenomenon whereby an individual with an attribute which is deeply discredited by his or her society is rejected as a result of the attribute" (Goffman, 1963), is an issue particularly impacting on persons with ID (Scior et al., 2016). Tools specific for measuring perceived stigma in this patient group have been developed, but their testing has been limited, requiring replication from further studies (Ali, Strydom, Hassiotis, Williams, & King, 2008). Additionally, establishing whether persons with ID whom meet diagnostic criteria for ASD experience additional stigma relative to those who do not meet such criteria will be useful in providing further information pertaining to the life experiences of this patient group.

The Autism Quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) is a 50-item self-administered tool designed to measure the extent of the presence of traits associated with ASD in adults with normal intelligence. It has good test-retest and inter-rater reliability (Baron-Cohen et al., 2001) as well as discriminative validity (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005).

The Social Responsiveness Scale, 2nd edition – Adult (SRS-2) (Constantino & Gruber, 2012) is a 65-item questionnaire, consisting of both self and informant report versions, designed to assess ASD traits in adults of normal intelligence. It covers five domains, including social awareness, social cognition, social communication, social motivation and restricted interests and repetitive behaviour (Baghdadli, Russet, & Mottron, 2017). The informant report version will be used in the SPRINT study. Studies involving the Japanese (Takei et al., 2014), German (Bölte, 2012) and English (Chan, Smith, Hong, Greenberg, & Mailick, 2017)

versions of the SRS-2 have demonstrated mixed evidence for convergent validity with other measures. Discriminative validity appears reasonable to good (Chan et al., 2017; Takei et al., 2014). A systematic review by Baghdadli *et al.* (2017) concluded that the SRS-2 had satisfactory internal consistency and structural validity, based on a moderate level of evidence (Bölte, 2012; Takei et al., 2014), though a more recent study suggests higher levels of internal consistency (Chan, Smith, Hong, Greenberg, & Mailick, 2017).

The Adult Social Behaviour Questionnaire (ASBQ) (Horwitz et al., 2016), consisting of both self- and other- report versions, measures ASD features across six domains (reduced contact, reduced empathy, reduced interpersonal insight, violation of social conventions, insistence on sameness and sensory stimulation/ motor stereotypies). Early findings (Horwitz et al., 2016) suggest that the ASBQ is able to reliably detect milder variants of ASD, as well as differentiate those with ASD from both non-clinical groups as well as patients with other psychiatric diagnoses.

The EuroQol-5D-5L (EQ-5D-5L) (Herdman et al., 2011) is a widely-used self-report instrument that measures general health, using five levels of severity across five dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Additionally, respondents are also required to rate their overall health (on the day of questionnaire completion) from 0-100, using a Visual Analogue Scale (the EQ-VAS). The EQ-5D-5L appears to demonstrate superior discriminatory power and convergent validity relative to the previous three-level version of the questionnaire, the EQ-5D-3L (Janssen et al., 2013).

The Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing, Leekam, Libby, Gould, & Larcombe, 2002) is a 320-item semi-structured interview schedule designed for use with a parent or carer of an individual, in order to obtain information relevant to the person's behaviours and needs, as well as eliciting information relating to the features of

ASD. The DISCO has previously been used to study ASD in adult patients (Brugha et al., 2011). In this study we will be using only the 180 items that contribute toward the diagnostic algorithm, psychiatric conditions and forensic problems sections, hereafter referred to as DISCO-A, rather than the full 320-items in their entirety.

The Autism Diagnostic Observation Schedule version 2 (ADOS-2) (Lord et al., 2012), for which the algorithm was revised in 2014 (Hus & Lord, 2014) is a multi-module instrument used in the diagnosis of ASD's among both patients with ID (Sappok et al., 2013) and normal intelligence (Baghdadli et al., 2017). The Module 4 version (used in adolescents and adults who are verbally fluent) has well-established validity and predictive value in both research (de Bildt, Sytema, Meffert, & Bastiaansen, 2016; Pugliese et al., 2015) and clinical (Langmann, Becker, Poustka, Becker, & Kamp-Becker, 2017; Maddox et al., 2017) settings. In patients with ID, whom often have reduced expressive language abilities, Modules 1, 2 and 3 can be used as an alternative means of assessment, depending on the level of impairment (Brugha et al., 2016; Sappok et al., 2013). For the SPRINT study, the Module 4 version will be used in Phase 2 for all participants without ID; for participants with ID, the assessing member of the research team will make a professional judgment as to which Module (1, 2, 3 or 4) is most appropriate, based on the participants level of verbal fluency and intellectual functioning.

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization, 1994) is a set of manuals for measurement of psychopathology and behaviours associated with mental illness. The second version demonstrated moderate-substantial reliability and high sensitivity and specificity, when subjects rated videotaped interviews by experts (Rijnders et al., 2000). The third version (SCAN-3), currently in development, will have a Neurodevelopmental Section; within this will be an ASD interview subsection (ASD-SCAN-3).

The Adult Psychiatric Morbidity Survey (APMS) (McManus, Bebbington, Jenkins, & Brugha, 2016) consists of community, general population data pertaining to the prevalence of psychiatric disorders in adults (both treated and untreated, and defined as being aged ≥16 years) living in England. The 2014 APMS is the fourth in the series, having previously been conducted in 1993, 2000 and 2007. For the 2014 APMS, approximately 7,500 adults were interviewed. For the SPRINT study, the Physical Health Conditions and Mental Illness Diagnoses and Treatment sections of the 2014 APMS will be used to interview Phase 2 participants about their physical and mental health respectively.

The Stigma Questionnaire for people with Intellectual Disability (SQID) (Ali et al., 2008) is a 10-item scale for measuring stigma in patients with ID. It has face and content validity, as well as having been developed with a view to accommodating for the cognitive deficits present in this patient group (Werner, Corrigan, Ditchman, & Sokol, 2012). This scale was added to the project protocol following consultation with patients with ID and their carers, whom advised that stigma was an issue of particular importance to them and requested that it be incorporated into the study.

The major internationally recognised diagnostic criteria for ASD include those of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems Diagnostic Criteria for Research [ICD-10-DCR] (World Health Organization, 1993) and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5] (American Psychiatric Association, 2013). Checklists for both of these sets of criteria will be completed by the assessing member of the research team for all Phase 2 participants, to establish whether the patient satisfies such criteria.

2.4. Aims:

1. To estimate the prevalence of ASD's amongst adults who have been admitted to psychiatric hospitals (including those with intellectual disabilities).

2. To examine the association between other mental and physical health conditions in adults who meet diagnostic criteria for ASD's with those who do not meet such criteria (all of whom have been admitted to a psychiatric hospital) and other psychiatric and physical comorbidities within an adult psychiatric inpatient population.

2.5. Objectives:

The objectives of the study are:

1. Undertake ASD testing of a large adult psychiatric inpatient population, through the use of validated test questionnaires, including the Autism Quotient (AQ), the informant version of the Social Responsiveness Scale, 2nd edition – Adult (SRS-2) and the Adult Social Behaviour Questionnaire, (ASBQ, both the self [ASBQ-S] and informant [ASBQ-I] versions).[3]
2. Invite a subgroup of these patients, selected via stratified random sampling according to AQ questionnaire score, to undergo comprehensive ASD diagnostic criteria testing with the Diagnostic Interview for Social and Communication Disorders (DISCO-A), the Autism Diagnostic Observation Schedule version 2 (ADOS-2), the ASD interview within the Schedules for Clinical Assessment in Neuropsychiatry version 3 (ASD-SCAN-3).[4] Whether the patient satisfies diagnostic criteria for ASD will be

[3] Participants with ID will not undergo these tests (Phase 1), instead progressing to comprehensive ASD diagnostic criteria testing automatically, rather than by virtue of their AQ score.
[4] Participants with ID will not undergo ASD-SCAN-3 testing, as it has not been developed for intended use in this patient group.

determined following the testing process, through the use of ICD-10-DCR and DSM-5 diagnostic criteria checklists.

3. Collect details regarding the experience of stigma in patients with ID, using the Stigma Questionnaire for people with Intellectual Disability (SQID).[5]
4. Collect additional data pertaining to psychiatric and physical health comorbidity, on Phase 1 (non-ID) patients and their informants, through use of the EuroQol-5D-5L (EQ-5D-5L), and on all Phase 2 patients through use of the Mental Illness Diagnoses and Treatment and Physical Health Conditions sections of the 2014 Adult Psychiatric Morbidity Survey (APMS).

2.6. Outcomes:

1. The primary outcome measure for the study will be the absence or presence of meeting internationally agreed diagnostic criteria for ASD.
2. The secondary outcome measure will be extent of other mental and physical health conditions in adults in who meet diagnostic criteria for ASD's, compared with those who do not meet such criteria.

2.7.Research Plan:

2.7.1. Workstream I

Aim:

To estimate the prevalence of ASD's among adult psychiatric inpatients (including those with intellectual disabilities).

[5] To be undertaken by participants with ID only.

Description:

This workstream will utilise a multi-phase cross-sectional design, whereby a large number of psychiatric inpatients will be tested for likelihood of ASD's with self- and informant-administered questionnaires (Phase 1- AQ, SRS-2, ASBQ-S, ASBQ-I and a basic information form), and a smaller group of patients, selected via stratified random sampling according to AQ questionnaire score (Table 2), will undergo further comprehensive diagnostic evaluation via interview-based assessment by a qualified health professional (Phase 2- DISCO-A, ADOS-2 and ASD-SCAN-3). This is a single centre study, where we will work with health professionals across at least two acute psychiatric hospital sites that are part of the same centre, the Bradgate Mental Health Unit (focussing only on the adult acute mental health wards within this site[6]) and the Agnes Unit (a unit comprised solely of specialist acute mental health wards for patients with ID), both based in Leicester, UK. Psychiatric inpatients with ID will bypass Phase 1 questionnaire testing (with all participants progressing directly to Phase 2), as well as ASD-SCAN-3 testing in Phase 2, owing to these tests having not been validated and/or developed for use in this patient group. They will be instead tested with a stigma scale, the SQID. For participants with ID, the assessing member of the research team will make a professional judgment as to which ADOS Module (1, 2, 3 or 4) is most appropriate to use, based on the participants level of verbal fluency and intellectual functioning. This is in contrast to participants without ID, whom, if participating in Phase 2, will all be assessed with ADOS Module 4. Whether the patient satisfies diagnostic criteria for ASD will be determined following the Phase 2 testing process, through the use of ICD-10-DCR and DSM-5 diagnostic criteria checklists by the assessing member of the research team.

[6] Bradgate Mental Health Unit has other types of inpatient wards, including for eating disorders, forensic psychiatry, older person's psychiatry and a psychiatric intensive care unit. Patient's admitted to these other units will not be participating in the study.

Table 2: The probability of selection for Phase 2 according to AQ questionnaire score. This probability framework for the AQ has been validated in a previous study conducted on adult participants from a mixture of inpatient and community mental health settings (Tyrer et al., 2013). Participants with high AQ scores will have a greater probability of selection.

Questionnaire score	Probability of selection
Total AQ score	
≤19	0.1
20-24	0.2
25-29	0.3
30-39	0.6
≥40	1.0

Target Population:

People aged between 18 to 65 years (i.e. adult patients) whom have had an inpatient stay on an acute mental health ward in a psychiatric hospital. To ensure the population is representative, a cross section of all such inpatients[7] over a defined time period will be invited to take part. This time period will likely be around 6-9 months, as the two units have an approximately combined 1000 patient admissions per year.[8]

Inclusion and Exclusion Criteria:

Inclusion criteria for the study include being between 18 to 65 years of age (on the date of psychiatric hospital admission) and being or having been a psychiatric inpatient on an adult acute mental health ward at either the Bradgate Mental Health Unit or the Agnes Unit (both based in Leicester, UK) during a predefined time period. These units serve a population of

[7] Except in instances where their responsible clinician does not consent to their participation.
[8] Figure obtained through liaison with the Leicestershire Partnership NHS Trust medical director Professor Mohammed Al-Uzri. Though the sample size required is 200 participants, previous similar studies suggest that 43-75% of potential participants will refuse to participate in the study (Tyrer et al., 2013). This is discussed at greater length in the next subsection, entitled 'Sampling and Sample Size.

approximately 1 million people living in both urban and rural areas within Leicester, Leicestershire and Rutland (Leicestershire Partnership NHS Trust, 2018).

Exclusion criteria include patients under the age of 18 years, over the age of 65 years and/or having no history of being a psychiatric inpatient. Patients with a clinical diagnosis of dementia will be excluded on the basis of the practical difficulties of conducting ASD testing in this patient group (van Niekerk et al., 2011); patients will not be excluded on the basis of any other clinical conditions. Also, patients lacking capacity will be excluded if they become distressed by the assessment process (at any point) or if their guardians are not in agreement with them remaining in the study. Participants also need to be able to understand written and/or verbal English.

Sampling and Sample Size:

Participants satisfying inclusion criteria will be recruited prospectively from psychiatric hospital sites within Leicestershire Partnership NHS Trust, via a member of their direct healthcare team inviting them into the study. If the participant wishes to find out more, they would subsequently complete an expression of interest form, providing permission to be contacted by a member of the research team, as well as their contact details. The exception to this approach will be in instances where a member of the research team is a member of the direct healthcare team of the patient[9]; in such instances the research team member will approach such patients directly.

Healthcare team members of both inpatient units will be invited to a talk to introduce the study, as well as having such details sent out to them via the Leicestershire Partnership NHS

[9] Based on the current research team, this situation would apply to all inpatients of Watermead Ward at the Bradgate Mental Health Unit (where Professor Mohammed Al-Uzri is their responsible clinician) and all inpatients of the Agnes Unit (where Dr Sam Tromans is a member of the healthcare team).

Trust communications team. Additionally, recruitment posters will be on display at both mental health units.

Phase 1 testing will involve about 200 patients (and corresponding informants), whereas Phase 2 testing will involve about 40 patients. Previous similar studies conducted locally have shown that around 75% of potential participants either refuse to take part or initially consent but do not complete the questionnaires when approached in the outpatient/community setting, though this proportion falls to approximately 43% when such individuals are approached in the inpatient unit setting (Tyrer et al., 2013). For this reason, approximately 600 patients will be invited into Phase 1, with a view to obtaining Phase 1 data for 200 participants. In the event that Phase 2 recruitment is inadequate to obtain 40 participants, the probabilities of selection (Table 1) will be revised, with a view to increasing the number of participants selected for Phase 2; this decision will be made around 6 months into the field work, which is to last a total of 24 months. Participants with ID will not be subjected to Phase 1 questionnaire testing, instead progressing directly to Phase 2 (though workstream II clinical data will be collected in all instances).

Setting:

Participants will be approached by a member of their direct healthcare team either during their inpatient hospital stay (where they will be approached at the hospital site) or contacted following their discharge from hospital. Phase 2 assessments will take place either at a Leicestershire Partnership NHS Trust hospital site, the University of Leicester or the patient's home, depending on the participant's preferences, their current clinical needs and relative availabilities of the aforementioned sites.

Data Collection and Analysis:

We will collect information from a combination of Phase 1 test completion from patients and informants and Phase 2 clinical assessment of a subgroup of these patients, conducted by the research team. Phase 1 test data will take the form of the completed questionnaires, returned either via post or collected from the patients acute mental health ward (in instances where the patients are still hospital inpatients at the time of completing these tests). Phase 2 clinical assessment data will be recorded on the relevant paper forms pertaining to the tests (DISCO-A, ADOS-2, ASD-SCAN-3 and SQID). The sequence in which these tests (as well as the APMS sections – see Workstream II) are administered will be random, to address any bias associated with interview order. The data on both the Phase 1 questionnaires and Phase 2 paper forms will be transferred to a Microsoft Excel spreadsheet on a Leicestershire Partnership NHS Trust or University of Leicester computer.

Primary Measures:

- ASD assessment information: 1) Questionnaire findings – AQ, SRS-2, ASBQ-S and ASBQ-I; 2) Clinical assessment findings – DISCO-A, ADOS-2, ASD-SCAN-3, SQID[10], and ICD-10-DCR and DSM-5 ASD diagnostic criteria.

Analysis (Prevalence):

The purpose of analysis will be to estimate the overall prevalence of ASD's within the Leicestershire adult psychiatric inpatient population. This will be calculated based on the proportion of Phase 2 participants who meet the ICD-10-DCR and DSM-5 diagnostic criteria for ASD's on clinical assessment, with adjustment for selection and non-response, as well as the different study designs for the ID and non-ID patient subgroups. Microsoft Excel, as well as a dedicated statistical software package – either SPSS or R – will be used to assist data analysis.

[10] Not part of the ASD assessment itself directly, but rather a measure of stigma, incorporated following consultation with patients with ID and their carers.

Blinding:

The study will be completed under double-blind conditions, whereby neither the patients nor the health professionals completing the Phase 2 clinical assessment will have knowledge of the patient's corresponding Phase 1 test findings. Parties who may be aware of the Phase 1 test findings will be asked not to share this information with the health professionals involved in the diagnostic assessment process. Where such information is inadvertently shared, the parties involved will be asked to report such incidents to the research team.

2.7.2. Workstream II

Aim:

To examine the association between ASD's and other psychiatric and physical comorbidities among the adult psychiatric inpatient population.

Description:

This workstream will collect clinical data for all patients included in Phase 2 of the SPRINT study.

Target Population, Inclusion and Exclusion Criteria and Sampling and Sample Size:

All participants included in Phase 2 of workstream I will be included in workstream II.

Setting:

Participant data will be obtained via participants completing a standardised interview, conducted when they attend for Phase 2 testing.

Data Collection and Analysis:

Data will be collected using a standardised interview, which will be completed with participants as part of the Phase 2 testing process. This interview will be comprised of several questions pertaining to their basic information and mental health, as well as the Mental Illness Diagnoses and Treatment and Physical Health Conditions sections of the 2014 APMS. For participants with ID, they may require the assistance of their accompanying informant/carer. Additionally, patients without ID will complete a basic information form as part of the Phase 1 testing process. The data from these forms will then be transferred to a Microsoft Excel spreadsheet.

Secondary Measures:

- Basic Information: 1) Date of birth 2) Sex 3) Postcode 4) Ethnic group 5) Employment status 6) Relationship status
- Mental Health (Psychiatric) History: 7) Date of most recent psychiatric hospital admission 8) Discharge date of most recent psychiatric hospital admission (where applicable) 9) Total number of inpatient psychiatric admissions 10) The Mental Illness Diagnoses and Treatment section of the 2014 APMS
- Physical Health (Medical) History: 11) The Physical Health Conditions section of the 2014 APMS
- General Health: 12) The EQ-5D-5L[11]

Analysis (Comorbidity):

The primary purpose of analysis will be to describe the characteristics of the Phase 2 population (including the overall population, those found to meet ASD diagnostic criteria on testing and those found to not meet ASD diagnostic criteria on testing), as well as

[11] To be undertaken by non-ID patients and their informants only.

establishing the prevalence's[12] of the psychiatric and physical health comorbidities described in the respective APMS sections (Table 6) in those who do (and do not) meet diagnostic criteria for ASD on Phase 2 testing. Univariate analysis will be carried out for individual comorbidities, to identify the level of their association with meeting the ICD-10-DCR and DSM-5 diagnostic criteria for ASD, relative to those who do not meet such criteria, as well as corresponding OR, 95% CI and p-values[13]. As for workstream I, Microsoft Excel, as well as a dedicated statistical software package – either SPSS or R – will be used to assist in data analysis.

Table 6: The psychiatric and physical health conditions outlined in the corresponding sections of the 2014 APMS (McManus, Bebbington, Jenkins, & Brugha, 2016).

Mental Illness Diagnoses and Treatment Section	Physical Health Conditions Section
• A phobia • Panic attacks • Post-traumatic stress disorder • ADHD or Attention Deficit Disorder (ADD) • Bipolar disorder (or 'manic depression') • Depression • Post-natal depression • Dementia (including Alzheimer's) • An eating disorder • Nervous breakdown • A personality disorder • Psychosis or schizophrenia • OCD	• Cancer • Diabetes • Epilepsy/ fits • Migraine or frequent headaches • Dementia or Alzheimer's disease • Cataracts/ eyesight problems • Ear/ hearing problems • Stroke • Heart attack/ angina • High blood pressure • Bronchitis/ emphysema • Asthma • Allergies • Stomach ulcer or other digestive problems

[12] In the case of psychiatric comorbidities, we will be looking at lifetime prevalence, whereas for physical health comorbidities we will be looking at prevalence since that age of 16 years, in keeping with the methodology of the APMS 2014 survey, and potentially enabling later comparison of SPRINT study comorbidity data with 2014 APMS data.

[13] To establish whether there are statistically significant ($p=<0.05$) differences between those participants meeting diagnostic criteria for ASD on Phase 2 testing, in comparison to those who do not meet said criteria.

• Seasonal affective disorder • Alcohol or drug dependence • Any other anxiety disorder • Any other mental, emotional or neurological problem or condition	• Liver problems • Bowel/ colon problems • Bladder problems/ incontinence • Arthritis • Bone, back, joint or muscle problems • Infectious disease • Skin problems • Other (please specify)

Blinding:

The health professionals assessing participants in Phase 2 will be blinded to the Phase 1 assessment findings (i.e. questionnaire data from workstream I). Parties who may be aware of such findings will be asked not to share this information with the health professionals completing Phase 2 interview-based assessments. As for workstream I, where such information is inadvertently shared, the parties involved will be asked to report such incidents to the research team.

2.8. Statistical Review:

The statistical aspects of the study, including sample size, have been reviewed by statisticians based at the University of Leicester (Dr Nicola Spiers and Dr Maria Viskaduraki). The sample size was calculated through the use of a statistical textbook and related software (Machin, Campbell, Tan, & Tan, 2011), whereby for a significance level of 0.05 and power of 85%, assuming estimates of 1% community ASD prevalence and 5% inpatient ASD prevalence (Tromans, Chester, Kiani, Alexander, & Brugha, 2018), a required sample size of 374 patients is required.

Ideally, we would be subjecting a minimum of 374 patients to Phase 2 testing. This is because only participants completing Phase 2 interview assessments will yield data pertaining

to the primary outcome variable (i.e. the presence of absence of satisfying diagnostic criteria for ASD). However, this is not feasible owing to resource limitations. For this reason, around 40 patients (from the minimum of 200 subjected to Phase 1 testing) will be selected, via stratified random sampling, for Phase 2 testing. Our results will be based on the assumption that the data for these 40 patients is representative of the larger group subjected to Phase 1 testing. Owing to the aforementioned sample size, the SPRINT study should be considered a pilot/feasibility study, with a view towards potential expansion of the study population upon its completion.

2.9. Consent:

Over a designated time period, potential participants will be contacted via members of their direct healthcare team based within acute mental health wards on the two sites. The research team will then contact individuals whom have consented to be contacted by them, with a view to providing further, more comprehensive study information.

This information will explain the purpose and nature of the study, what their involvement would entail and the alternatives to taking part. The entirely voluntary nature of taking part in this study will be emphasised, as well as the option to withdraw from the study at any time. Additionally, all potential participants will have the opportunity to ask any further questions about the study to the research team.

Though informants are not disclosing information about themselves in this study, but rather reporting their view about the patients, they also will be consented for both phases of the study and will have the same rights as research participants as the patient members.

For Phase 1 participation, consent will be undertaken in person (following participants completing expression of interest forms, indicating consent to be contacted by a member of the research team). The member of the research team will discuss the study further, explaining what is expected of them, checking their level of understanding and answering any questions. They will also assess the ability of the participant to complete the Phase 1 questionnaires in a meaningful manner, via testing with a sample of seven specimen questions (similar to, but not the same as, those featured within the AQ, ASBQ-S and EQ-5D-5L questionnaires). If the participant is still interested in participating, the research team member will then provide a study information pack, as well as the Phase 1 questionnaires and a study consent form in a pre-paid envelope. Upon receipt of the signed consent form by the research team, they will countersign the form and return a copy to the patient (retaining one copy for their own records).

For Phase 2 participation, participants will be contacted either via telephone or in person to inform them of their selection and invite them and their informant for a meeting in person with a member of the research team. All participants will be seen in person by a member of the research team as part of the consenting process for Phase 2. This is for the purposes of assessing their capacity and that, where they lack capacity, ensuring that appropriate personal consultee arrangements are in place and followed. The consenting process will involve assessing whether the participant has capacity to consent in accordance with the Mental Capacity Act (2005) (Department of Health, 2005). This involves a 2-stage test of capacity, including firstly establishing whether the participant has an impairment of their mind or brain, and secondly whether such an impairment (if present) means that the participant is unable to make a specific decision (such as participating in Phase 2) when required. The Mental Capacity Act requires individuals to be able to understand the decision to be made, retain information pertinent to the decision, weigh such information up in making their decision,

and be able to communicate their decision. All research team members will have relevant training and experience in assessment of mental capacity.

For both phases of the study, the participant will be allowed as much time as they wish (and no less than 24 hours for Phase 1) to consider the information, and the opportunity to question the investigator, their GP or other independent parties to decide whether they will participate in the study. Participants will be advised that they can withdraw from the study at any time. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief and Principal Investigator, as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Trial Master File. A copy of the signed Informed Consent will be given to participants and a copy retained by the research team.

Adults lacking capacity to consent for themselves will be included where possible. This is because in order to reliably estimate the prevalence of ASD's in an adult psychiatric inpatient setting, it is important to include as representative a study population as possible. Exclusion of potential participants lacking capacity would likely exclude a subgroup of patients that are disproportionately more (or less) likely to have ASD's than those with capacity. For example, patients with ID have a greater likelihood of lacking capacity, and thus exclusion of those without capacity would impact on the reliability of the results pertaining to this patient group. Additionally, the nature of the procedures utilised in this study are all non-invasive and unlikely to cause significant harm to the participants concerned. Nevertheless, if the procedures were to cause the participant significant distress and/or the participants' guardian no longer wished for them to remain in the study, they will be withdrawn from the study. Any data collected up until the point of withdrawal will be retained and used in the study analysis.

In circumstances whereby a participant lacks capacity to consent to take part in the study, a personal consultee will be identified to act on their behalf. This individual would be someone who cares for the participant or is interested in their welfare (likely either an unpaid carer, long-term partner or close relative), and is prepared to be consulted. The personal consultee will be informed about all aspects of the study which are relevant to their decision, including being provided with relevant information, given time to make a decision, and being able to ask questions to a member of the research team. Additionally, despite their lack of capacity, as much information as possible (in a form of communication that they can best understand) will be provided to the participant. Wherever possible, the study procedures will also be conducted in a setting that is familiar to the patient, such as their home, to minimize their discomfort and inconvenience. If their continued participation is causing them significant distress, they will be withdrawn from the study. Similarly, if their personal consultee is not in agreement with their continued participation, they will be withdrawn from the study. Any data collected up until the point of withdrawal will be retained and used in the study analysis.

In the event that a participant should lose capacity to consent during the study, their initial consent would not legally endure, and an appropriate personal consultee would need to be found before potentially continuing with the study.

2.10. Payments:

For Phase 1, participants and informants will each receive a £5 high street gift voucher as payment for their participation in the study. For Phase 2, both participants and informants will receive £15 high street gift vouchers as payment for their participation in the study.
In situations where participants are required to travel, their travel expenses will be reimbursed. However, wherever possible, the member of the research team will travel to the

residence of the participant (or the hospital in cases where they remain an inpatient at this time).

2.11. Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) and the host institution for written approval.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

2.12. Research Ethics Committee Review and Reports:

Before the commencement of the study, a favourable opinion will be sought from a Research Ethics Committee for the study protocol and all other relevant documents. All correspondence with the Research Ethics Committee will be retained by the research team. Patients will only be enrolled on the study following all appropriate approvals having been obtained from the relevant participating organisations.

An Annual Progress Report will be submitted to the Research Ethics Committee within 30 days of the anniversary date on which the favourable opinion was given; this will be on an annual basis until the study has ended. The chief investigator (Dr Sam Tromans) will be responsible for production of these reports.

In the event that the study is ended prematurely, the chief investigator will notify the Research Ethics Committee, explaining the reasons for the termination. Within one year of

the study ending, the chief investigator will submit a final report to the Research Ethics Committee, including the results and any related publications.

2.13. Potential Amendments:

Potential amendments to the protocol can be put forward by the members of the research team (Dr Sam Tromans, Dr Reza Kiani, Dr Regi Alexander, Professor Mohammed Al-Uzri and Professor Terry Brugha) or the sponsoring organisation. In the event that an amendment to the Research Ethics Committee application or related documents was being proposed, this would be first be discussed with the steering group and sponsor. If the proposed amendment was then deemed appropriate or even necessary, the appropriate documentation (including an updated protocol) would be signed off by the sponsor and sent to the Research Ethics Committee for consideration. Substantial amendments requiring Research Ethics Committee review will not be implemented until such a review has taken place and the related amendments have been approved.

2.14. Peer Review:

This protocol has been reviewed by all members of the research team, as well as individuals representing both the sponsor (University of Leicester) and the healthcare trust within which the study will be conducted (Leicestershire Partnership NHS Trust). This protocol has also been reviewed by the National Institute for Health Research [NIHR] Clinical Research Network (Institute for Mental Health Building, Triumph Road, Nottingham), for which Senior Investigator Award funding was subsequently awarded by Professor Martin Orrell (Director of Institute for Mental Health and NIHR Senior Investigator).

2.15. Barriers to Success:

Potential logistical challenges in undertaking the project will be completing it on a part-time basis within the planned timeframe of four years, with the chief investigator's time equally divided between academic work and clinical training. Some patients may lack capacity to provide informed consent for the study, and best interest's decisions as well as discussion with the primary caregiver needs to be undertaken in such circumstances. It is essential to obtain data for an appropriate patient sample size in order for the study to have sufficient statistical power to yield meaningful results; input from medical statisticians has been essential in calculating this size, which needs to be attained through an effective recruitment strategy.

2.16. Project Management:

2.16.1. Sponsor:

The sponsor of this study is the University of Leicester. The contact on behalf of the sponsor is Dr Michelle Muessel. The research reference code for this study is 0684. All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines. The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (World Medical Association, 2004). The Investigator will ensure that this study is conducted in full conformity with relevant

regulations and with the ICH[14] Guidelines for Good Clinical Practice (1996; CPMP/ICH/135/95).

2.16.2. Steering Group:

This role of the Steering Group will be to monitor progress and provide oversight for the study. They will meet a minimum of five times over the course of the study, where the research team will report their progress and findings, as well as any logistical or ethical issues. The Steering Group members will include 1) the chair 2) the chief and principal investigator, 3) collaborators, 4) at least two people with ASD's (including at least one person with comorbid ID), 5) at least two professional carers or family members for people with ASD (including at least one person whom has cared for a patient with an ASD who has previously been an inpatient in a psychiatric hospital).

An initial steering group meeting will occur early in year 2, with two subsequent meetings during data collection (years 2 and 3), one during the analysis of study data (year 3-4) and a final meeting when commencing writing up of the related project dissertation and disseminating the project's findings (year 4).

2.16.3. Project Reviews:

Project reviews, involving the chief investigator and collaborators, will be on a quarterly basis, and be more focussed on day-to-day project management, as well as attainment of performance targets with regard to data collection.

[14] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

2.17. Ethical Issues:

In our opinion, the main ethical issues posed by this research are the burden on participants, maintenance of data security, confidentiality, non-release of individual data to participants, participants not receiving a clinical diagnosis of ASD, a need to collect basic information on individuals refusing to participate in the study, coercion and the dual role (clinician/researcher) of research team members. Each of these issues is discussed in turn below.

2.17.1. Participant Burden:

All participants without ID who consent for the study will be inconvenienced in completing the test questionnaires in Phase 1, which will take about 50 minutes for the patient (basic information form, Autism Quotient [AQ], Adult Social Behaviour Questionnaire – self version [ASBQ-S] and EuroQol-5D-5L [EQ-5D-5L]) and 40 minutes for the informant (Social Responsiveness Scale, 2nd edition [SRS-2], ASBQ- informant version [ASBQ-I] and EQ-5D-5L). Experience from previous similar studies shows that participants often find this an enjoyable and interesting experience, and feel satisfied about contributing to science. For Phase 2 testing, non-ID participants and their informants will be inconvenienced by around 3-4.5 hours (plus travel time where applicable) if they remain for the entire assessment (Autism Diagnostic Observation Schedule – second edition [ADOS-2], the diagnostic algorithm, psychiatric conditions and forensic problems items within the Diagnostic Interview for Social and Communication Disorders [DISCO-A], the ASD interview within the Schedules for Clinical Assessment in Neuropsychiatry – version 3 [ASD-SCAN-3] and the Physical Health Conditions and Mental Illness Diagnoses and Treatment sections of the Adult Psychiatric Morbidity Survey [APMS]), though only by 1-2.5 hours each if they only remain for their respective interviews. Participants with ID and their informants will be

inconvenienced by about 2-3 hours, though only by about 1-1.5 hours for the participant and 1.5-2 hours for the informant if they only remain for their respective interviews (participants with ID will not be undergoing ASD-SCAN-3 testing, though will be instead tested with the Stigma Questionnaire for people with Intellectual Disability [SQID]). To minimize such inconvenience, wherever possible these assessments will be conducted in the patient's homes.

2.17.2. Data security:

Participants will be advised regarding the security arrangements for storage of their data. This includes storage of personal data as paper files being stored in a locked security cabinet on an NHS hospital site and electronic files being stored in an NHS encrypted format, as well as stored on a cloud-based local portfolio management system. Link anonymised versions of the data will also be stored on NHS, University and personal computers. Participants will also be informed of the indemnity arrangements in the event that a data breach were to occur.

2.17.3. Confidentiality:

For both phases of the study, participants will be informed that their data is for examination of the research questions, and will not be stored in their clinical records. Information will only be shared with other professionals in the event that the participant discloses information that puts themselves and/or other persons at serious risk (the participant will be informed about this as part of the consent process for the study). The other circumstance where information will be stored in participant's records is if they specifically request for their Phase 2 data to be sent to their General Practitioner and/or Consultant Psychiatrist. Any safeguarding concerns will be addressed according to local trust guidelines (Leicestershire

NHS Partnership Trust). All research team members have undertaken Good Clinical Practice (National Institute of Health Research) training, as well as safeguarding training provided by their respective local healthcare trusts. Additionally, the principal and chief investigator will have access to his supervisors, whom collectively have extensive clinical experience with both ID and non-ID patient groups.

2.17.4. Non-release of individual Phase 1 data to participants:

This decision was taken as the test results in isolation may be confusing for the participant. For example, a participant scoring highly on the AQ may be under the mistaken perception that they have a diagnosis of an ASD when no diagnostic testing has actually taken place. We have detailed on the participant information sheets that individual participant feedback will not be provided for Phase 1 of the study.

2.17.5. Participants not receiving a clinical diagnosis of ASD:

This study is focussed on participants meeting internationally recognised criteria for ASD, rather than being given a clinical diagnosis. As such, individuals who may suspect themselves to have an ASD will not automatically receive an answer to this concern. However, all participants will still have access to their usual clinical care, and would still be able to pursue a diagnostic assessment for ASD's via an NHS clinic if inclined to do so. Additionally, if requested by the participant, those whom participate in Phase 2 can have their Phase 2 test results forwarded to their Consultant Psychiatrist and/or General Practitioner. This would help inform these professionals as to whether further assessment is required.

2.17.6. Anonymised Data of Overall Population:

Basic non-identifiable clinical data will be collected on all inpatients[15] based within the Bradgate Mental Health Unit and Agnes Unit during the study period, in order to identify differences between the study population and the inpatient population as a whole. This information will be obtained from the clinical coding team at Leicestershire NHS Partnership Trust, who collect such data on all adult inpatients. The data collected for these individuals will be as follows:

- Basic Information: 1) Year of birth 2) Sex 3) First part of postcode 4) Ethnic group 5) Employment status 6) Relationship status
- Mental Health (Psychiatric) History: 7) Date of most recent psychiatric hospital admission 8) Discharge date of most recent psychiatric hospital admission (where applicable) 9) Total number of inpatient psychiatric admissions 10) Mental health diagnoses (ICD-10; World Health Organization, 1992)
- Physical Health (Medical History): 11) Physical health diagnoses (ICD-10)

2.17.7. Coercion risks:

It is important that neither participants nor their responsible clinicians feels coerced into taking part in this research study. Participants will be informed during the consenting process that their participation in the study is entirely voluntary and will have no impact on their future clinical care. They will also be advised that they can withdraw from the study at any time. In terms of responsible clinicians, the relatively junior role (specialist registrar) of the principal and chief investigator Sam Tromans, should reduce the degree to which members of direct healthcare teams would feel obligated into providing permission for their patients to potentially take part.

[15] Via the Leicestershire Partnership NHS Trust clinical coding team.

2.17.8. Dual role of research team members:

The research team in its current form is comprised entirely of clinicians whom also engage actively in research, and would as such have 'dual roles' as both clinicians and researchers (Hart & Crawford-Wright, 1999). This can have potential benefits as well as challenges in terms of conducting the research. For instance, all members of the research team are qualified to make a clinical diagnosis of ASD. Traditionally, in such research projects, the data may have been collected by individuals unable to make such a clinical diagnosis, but this issue has been raised by patients and carers in Patient and Public Involvement forums pertaining to this study. The most appropriate compromise we feel is that Phase 2 (diagnostic assessment) participants whom have concerns about problems with social communication (either pre-existing concerns or raised via participation in the study) can elect to have their assessment reports forwarded to their Consultant Psychiatrist and/or General Practitioner if they wish for this to happen (please note that the default approach will be that such reports will not be forwarded, though the participants will be advised of this alternative option). Additionally, there is a potential risk that the researcher conducting the assessment could be involved in the regular clinical care of the research participant. This will likely apply to a relatively small number of participants, as the chief and principal investigator currently works exclusively with patients with ID clinically, whom will represent a relatively smaller portion of the study population. However, it is particularly important in such instances to emphasise the entirely voluntary nature of participation in this study.

2.18. Protocol Compliance:

Accidental deviations from the protocol can happen at any time, and will require documentation on the relevant forms, as well as being reported to the Chief Investigator. In

the case of serious breaches, the sponsor will also be informed. Frequently recurring deviations from the protocol, usually considered unacceptable, will require immediate action and could potentially be classified as a serious breach.

2.19. Data Protection and Patient Confidentiality:

All investigators and study site staff will be compliant with the requirements of the General Data Protection Regulation (Information Commissioners Office, 2018) and Data Protection Act 2018 (Great Britain, 2018) with regards to the collection, storage, processing and disclosure of personal information.

Participants will be assured that their data will only be accessible to members of the research team, as well as other National Health Service healthcare professionals and University staff, whom are bound by the same duties of confidentiality.

Source documents are original documents, data, and records from which participants' data are obtained. These include, but are not limited to, medical records, clinical and office charts, questionnaires and interview data. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant ID, not by name. Data will be stored in three settings:

- A locked cabinet based within a Leicestershire Partnership NHS Trust site. This will be in the form of hard (paper) copies of the consent, basic information, questionnaires and interview forms, as well as the screening and enrolment logs. This cabinet will be accessible to members of the research team only.
- On EDGE (Edge Clinical, 2017), a secure cloud-based local portfolio management system (as an incremental back-up system that will be backed up on a daily basis).

This system will be accessible to members of the research team only, and local implementation is owned and maintained by the East Midlands Clinical Research Network.

- On National Health Service and University computers in a depersonalised form, where all participant's identifying information will be replaced by their study ID (an unrelated sequence of characters). Such data files will be encrypted within password protected folders. These measures are designed to preserve confidentiality of data when shared with sponsors, co-investigators and other National Health Service and University professionals.

The data will be stored for a period of 5 years[16] after the study has ended. This is for several reasons. Firstly, the data may be useful with regard to other similar studies; in the event that the data were to be used for another project, Research Ethics Committee approval would be sought in the first instance. Consent forms and details of record linkage (i.e. study ID numbers) will be kept for 5 years as part of the research data so that in the event of the data being challenged, this will allow for verification of the quality of the data.

The data custodian for this study is Dr Sam Tromans.

2.20. Indemnity:

The University of Leicester insurance scheme will apply in meeting the potential legal liability of the sponsors for any harm to participants arising from the design or management of the research. The National Health Service indemnity scheme will apply in meeting the

[16] Paper files will be stored for only 3 years, whereas the cloud-based back-up of the data will be stored for 5 years.

potential legal liability of investigators and collaborators arising from harm to participants in the conduct of the research.

2.21. Access to the Final Study Dataset:

All members of the research team in its current form (Dr Sam Tromans, Dr Reza Kiani, Dr Regi Alexander, Professor Mohammed Al-Uzri and Professor Terry Brugha) will have access to participant data during the study. Access will also be permitted to other National Health Service professionals and University staff, whom are bound by the same duties of confidentiality; this will be detailed in the participant consent documentation. Additionally, data may be accessed by authorised individuals from the sponsor, regulatory authorities or the host site for monitoring and audit purposes. The sponsor operates a risk based monitoring and audit program to which this study will be subject.

2.22. Dissemination Policy:

The data arising from this study will be owned by the University of Leicester, the sponsoring organisation. All of the participating investigators will have rights to publish any of the study data. Funding and supporting bodies, including University of Leicester and Leicestershire Partnership NHS Trust, will be acknowledged in any resulting publications.

The systematic review underpinning our study (Tromans, Chester, Kiani, Alexander, & Brugha, 2018) has been published in a peer-reviewed journal (*Clinical Practice and Epidemiology in Mental Health*), as well as delivered as an oral presentation at an international conference (the 19th Congress of the Section of Epidemiology and Social Psychiatry of the European Psychiatric Association, held in Vienna, Austria in April 2018).

Upon completion of the study, the data will be analysed, with the production of a Final Study Report. This will be disseminated to participants and informants, whom we will liaise with beforehand, in order to develop materials that communicate our findings in an understandable way, to both ID and non-ID patient groups respectively. Participants will also have the option to specifically request results from the research team, who will aim to provide such information where it is not already detailed in the Final Study Report. Findings will also be distributed across the NHS to clinical teams as well as healthcare commissioning groups.

The findings of the study will also be disseminated via peer-reviewed journal publications, as well as national and international conference presentations. The Doctor of Medicine thesis pertaining to the study will be published online on the Leicester Research Archive (University of Leicester, 2018a) as per university policy.

2.23. Authorship Eligibility Guidelines:

All members of the research team in its current form (Dr Sam Tromans, Dr Reza Kiani and Dr Regi Alexander, Professor Mohammed Al-Uzri and Professor Terry Brugha) will be given authorship on the final study report. Authorship for any manuscripts will be in keeping with the authorship criteria outlined by The International Committee of Medical Journal Editors (2018).

2.24. Resources and Costs:

The chief and principal investigator is being funded by Leicestershire Partnership NHS Trust through a 4-year part-time (20 hours per week) Honorary Academic Clinical Lectureship based at the Social and Epidemiological Psychiatry Research Group, Department of Health

Sciences, University of Leicester. Basic costs for the study, including participant and informant payments, printing costs and pre-paid envelopes, will be paid for by a combination of the Social and Epidemiological Psychiatry Research Group and a £500 NIHR Senior Investigator Award.

2.25. Safety Reporting:

Due to the nature and design of the study, safety reporting does not apply. As such, adverse events and serious adverse events will not be collected or reported upon.

2.26. Protection of Intellectual Property:

The ASD-SCAN-3 interview forms part of the Phase 2 interview process for non-ID participants. This interview has not been formally published at this time. The ASD-SCAN-3 interview is a development of the background intellectual property embedded within the SCAN interview package, for which the copyright is held by the World Health Organization (WHO). The University of Leicester is a WHO designated SCAN Training and Reference Centre (University of Leicester, 2018b) and Professor Terry Brugha (Academic Supervisor of Dr Sam Tromans and SPRINT study research team member) is the lead for the Leicester SCAN programme as well as the chair for the WHO advisory committee for SCAN (University of Leicester, 2018c).

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4. APPENDICES:

4.1. Previous Studies on ASD Prevalence among Adult Psychiatric Inpatients

Author, year, location, reference	Total N enrolled in study	N screened	N indicated for diagnostic assessment	N subjected to diagnostic assessment	Details of excluded individuals	Male %	Mean age in years	Description of inpatient setting	Description of study population	Method of screening	Method of autism diagnosis	Diagnostic criteria used	Prevalence estimate	STROBE [17] score
Hare *et al.* (1999), England	1305	1305	240	215	Patients on trial leave to other placements were excluded. Also, some were excluded from initial screening for administrative reasons of no clinical significance. 96% of the special hospital population was screened.	86% (185/215) of those subjected to diagnostic assessment. Data pertaining to the male % of the 1305 individuals originally screened is not available.	41.8 (Age range 20-77 years)	Three secure psychiatric hospitals	All adults. Mixture of non-ID and ID patient, though details regarding the relative proportions of each are not provided within the article.	Autism Spectrum Disorder in Adults Screening Questionnaire (ASDASQ)[18] (Nylander & Gillberg, 2001).	Handicaps, Behaviours and Skills (HBS) schedule (Wing, 1980) and case note analysis.	ICD-10 (World Health Organization, 1992)	2.4% (31/1305), increased to 4.8% (62/1305) when equivocal cases are taken into account.	15/22
Mandell *et al.* (2012), USA,	141	141 (though all patients were	141	141	There were 348 residents within the hospital, so	75% (106/141)	52	State psychiatric hospital	Civilly committed patient. 32.6%	Social Responsiveness Scale (SRS) (Constantino	Four step process: 1-Historical charts and	DSM-IV[19] (Frances, 1994)	Overall: 9.9% (14/141). ID	16/22

[17] STROBE – Strengthening the Reporting of Observational Studies in Epidemiology (Vandenbroucke et al., 2007)

[18] Not referred to as the ASDASQ within the article itself, as the tool was (at the time of the Hare et al article being published) an unnamed, unpublished screening tool (which was later named the ASDASQ).

[19] Confirmed via correspondence with Dr David Mandell.

		subjected to diagnostic assessment irrespective of screening score)			only 41% were screened (141/308). Researchers attempted to obtain consent from all residents; 89% of refusal were passive (i.e. patient unable to give consent). Thus, non-capacitous individuals were excluded.				(46/141) patients had ID. Age range not given.	& Gruber, 2012).	electronic records reviewed; 2 – Diagnostic Interview for Genetics Studies (DIGS) (Nurnberger et al., 1994) conducted for each patient; 3 – Autism Diagnostic Interview – Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) completed by research reliable clinicians; 4 – case conference review by two independent teams		subgroup: 19.6% (9/46). Non-ID subgroup: 5.3% (5/95).	
Scragg and Shah (1994), England,	392	392	17	17, though 6 refused to be meet the investigator	Female patient excluded, on basis that Asperger's Syndrome is reporter to be much more common in males.	100% (392/392)	No data on age of study population, though the study population were adults.	Secure psychiatric hospital (Broadmoor, England)	Adult males. Unclear whether any patients in the study population had ID (details on IQ are only given for 9	Examination of case notes	Two stages (after initial screening stage): 1 – Screening Schedule for Autistic Behaviour (Part of the HBS interview	Gillberg and Gillberg (1989) (Gillberg & Gillberg, 1989) criteria	1.5% (6/392) (95% CI – 0.6 to 3.3%), increased to 2.3% with the addition of equivocal cases (However,	12/22

									patients whom met criteria for AS, none of whom had an IQ consistent with ID).		schedule) (Wing, 1980); 2 – Interview by the investigator.		this estimate was for Asperger's syndrome only, rather than all forms of ASD).	
Shah *et al.* (1982), England,	761	n/a	761	761	Exclusion of 129 patients, due to being non-mobile – 'their inability to walk unaided limited the possibility of their showing the behaviour pattern characteristic of classic Kanner's syndrome.'	61% (468/761)	No data for mean age available. Youngest patients were 16 years of age.	Long stay ID hospital[20]	The entire study population had ID.	n/a	Disability Assessment Schedule (Holmes, Shah, & Wing, 1982)	Details not provided within the article.	4% (27 to 34/761). The precise number of participants being diagnosed with ASD is not provided within the article, though they report a prevalence of 4% from a study population of 761.	12/22

[20] Referred to as a 'mental handicap hospital' within the source article.

4.2. Schedule of Procedures

Procedures	Stage		
	Initial stage	Approximately 0-6 months post commencement of data collection	Approximately 3-24 months post commencement of data collection
Informed consent	X		
Phase 1		X	
Phase 2			X

4.3. Amendment History

Amendment Number	Protocol Version Number	Date Issued	Author(s) of Changes	Details of Changes Made
Not applicable	1.0	15th November 2018	Not applicable	Not applicable
1	1.1	14th February 2019	Sam Tromans	Changes in accordance with those recommended by Research Ethics Committee review process, as well as addition of EuroQol-5D-5L and ADOS Modules 2-3 to study protocol.