## Welcome to the Integrated Research Application System

## IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

**Please enter a short title for this project** (maximum 70 characters)
Spectrum 10K

**1. Is your project research?**

(●) Yes ( ) No

**2. Select one category from the list below:**

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

(●) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

**If your work does not fit any of these categories, select the option below:**

( ) Other study

**2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?**

( ) Yes (●) No

**2b. Please answer the following question(s):**

| | | |
|---|---|---|
| a) Does the study involve the use of any ionising radiation? | ( ) Yes | (●) No |
| b) Will you be taking new human tissue samples (or other human biological samples)? | (●) Yes | ( ) No |
| c) Will you be using existing human tissue samples (or other human biological samples)? | ( ) Yes | (●) No |

d) Will the study involve any other clinical procedures with participants (e.g. MRI, ultrasound, physical examination)? ○ Yes ◉ No

**3. In which countries of the UK will the research sites be located?** *(Tick all that apply)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☐ Northern Ireland

**3a. In which country of the UK will the lead NHS R&D office be located:**

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

**4. Which applications do you require?**

- ☑ IRAS Form
- ☐ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

**Most research projects require review by a REC within the UK Health Departments' Research Ethics Service. Is your study exempt from REC review?**

○ Yes ◉ No

**5. Will any research sites in this study be NHS organisations?**

◉ Yes ○ No

**5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?**

**Please see information button for further details.**

○ Yes ◉ No

***Please see information button for further details.***

**5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?**

**Please see information button for further details.**

◉ Yes ○ No

*The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies*

*happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".*

*If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.*

**6. Do you plan to include any participants who are children?**

(●) Yes ( ) No

**7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?**

(●) Yes ( ) No

*Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.*

**8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?**

( ) Yes (●) No

**9. Is the study or any part of it being undertaken as an educational project?**

( ) Yes (●) No

**10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?**

( ) Yes (●) No

**11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?**

( ) Yes (●) No

**Integrated Research Application System**
**Application Form for Basic science study involving procedures with human participants**

## IRAS Form (project information)

*Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.*

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

**Short title and version number:** (maximum 70 characters - this will be inserted as header on all forms)
Spectrum 10K

*Please complete these details after you have booked the REC application for review.*

**REC Name:**
HSC REC A

**REC Reference Number:**
20/NI/0084

**Submission date:**
03/06/2020

## PART A: Core study information

### 1. ADMINISTRATIVE DETAILS

**A1. Full title of the research:**

Spectrum 10K - Common Variant Genetics of Autism and Autistic Traits (GWAS).

**A3-1. Chief Investigator:**

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | | [redacted] |

| | |
|---|---|
| Post | Professor of Developmental Psychopathology |
| Qualifications | M.Phil,PhD |
| ORCID ID | [redacted] |
| Employer | University of Cambridge |
| Work Address | Autism Research Centre<br>Douglas House<br>18B Trumpington Road, Cambridge, UK |
| Post Code | CB2 8AH |
| Work E-mail | [redacted] |
| * Personal E-mail | [redacted] |
| Work Telephone | [redacted] |
| * Personal Telephone/Mobile | [redacted] |

Fax

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
*A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.*

**A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?**
*This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.*

| | Title Forename/Initials Surname |
|---|---|
| | [redacted] [redacted] [redacted] |
| Address | Cambridge & Peterborough Foundation Trust |
| | Research & Development |
| | Addenbrooks Hospital |
| Post Code | CB2 0QQ |
| E-mail | [redacted] |
| Telephone | [redacted] |
| Fax | |

**A5-1. Research reference numbers.** *Please give any relevant references for your study:*

| | |
|---|---|
| Applicant's/organisation's own reference number, e.g. R & D (if available): | N/A |
| Sponsor's/protocol number: | |
| Protocol Version: | 1.0 |
| Protocol Date: | 20/04/2020 |
| Funder's reference number (enter the reference number or state not applicable): | [redacted] |
| Project website: | www.spectrum10k.org |

**Registry reference number(s):**
*The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.*

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):

**Additional reference number(s):**

| Ref.Number Description | Reference Number |
|---|---|

**A5-2. Is this application linked to a previous study or another current application?**

(●) Yes ( ) No

*Please give brief details and reference numbers.*
The study includes AWI participants in Scotland. A joint REC application is being made to Scotland A-REC.
IRAS Ref: 277521
REC Ref: Pending

## 2. OVERVIEW OF THE RESEARCH

***To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.***

**A6-1. Summary of the study.** *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Autism is a neurodevelopmental condition diagnosed in 1 to 2% of the population worldwide, with approximately 700,000 people on the autism spectrum in the UK. It is often diagnosed with other co-occuring conditions, including intellectual disability and epilepsy, and is associated with increased levels of mortality, unemployment and suicidal behaviour. There is a need to understanding the biological and environmental contributions to autism, co-occuring conditions, and wellbeing in autistic individuals.

To this end, the Spectrum 10K study is a re-contactable resource that aims to recruit at least 10,000 autistic individuals diagnosed by a qualified professional and, where possible, up to their third degree relatives to identify genetic and environmental factors that contribute to autism and related conditions. This will help us to accelerate understanding of the biological and environmental factors that contribute to the well-being of autistic individuals. As part of this, we also want to understand the effect of the recent COVID-19 pandemic on the autism community and how it is impacting health and wellbeing of autistic individuals.

Participants (or consultees) will register for the study online at the Spectrum 10K study website. Once a participant (or consultee) has read the participant information sheet and completed an online consent form, they will be asked to complete a mandatory baseline questionnaire. They will also be asked to complete an questionnaire about COVID-19 (optional). They will have the opportunity to complete further optional questionnaires straight away or later if they wish. A DNA saliva kit will be sent to participants and they will be asked to provide a saliva sample and return it for extraction of their DNA and analysis.

**A6-2. Summary of main issues.** *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

*Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.*

1. Vulnerable population
The Spectrum 10K cohort will include individuals with a professional diagnosis of autism with and without intellectual disability, or non-autistic individuals with co-occurring intellectual disability who are relatives of participating autistic individuals. The cohort will also include autistic and non-autistic children (individuals under 16 years of age). Finally, many autistic individuals may also have other co-occurring psychiatric or medical conditions.

To assess capacity to consent, appropriate measures will be put in place to protect and facilitate the population cohort in line with the Mental Capacity Act 2005. Measures will include the British Medical Association "Assessing Mental Capacity Tool" which will be available at the study website, the provision of adapted participant information sheets for adults with reduced capacity, and the
the availability of family member/advocate/carer assent within the consent procedure. If participants attend a research site, they will be assisted by a clinician or their care team to complete study registration and the baselines questionnaires. Swab-based saliva kits will be provided for individuals who are unable to spit.

For children, informed consent will be obtained from their parent or guardian. Questionnaires have been adapted for parents to complete about their child. Swab-based saliva kits will be provided for children who are unable to spit.

To ensure participants are not harmed during the study, sensitive questions can be skipped, and all participants will be signposted to helplines and charities should they feel distressed.

2. Saliva sample provision
To minimize distress, DNA will be collected from all participants using saliva samples which is less intrusive than providing a blood sample. All saliva sample kits will include an illustrated leaflet providing concise instructions for

using and returning the saliva kit for analysis. Participants will have the option to request assisted DNA collection kits (swabs instead of spitting). These kits may be easier for some participants to use if they are unable to spit or have difficulty doing so. Assisted kits use foam swabs which can be used to collect saliva. These kits may be particularly useful for participants with intellectual disabilities and for young children.

3. Questionnaire completion
Some participants may find completing the questionnaires burdensome. All participants will be asked to complete a baseline questionnaire which is comprised of two parts:
- the Developmental and Medical History Questionnaire which asks about education, occupation, physical and mental health, lifestyle, sleep, and gut health
- a questionnaire that measures autistic traits

The baseline questionnaire takes approximately takes 20 - 30 minutes, and can be saved at any point and returned to later.

COVID-19 Questionnaire (optional).
All participants will have the option to complete a questionnaire about COVID-19 if they choose to. If they are happy to complete the questionnaire, they will be asked to repeat the every 3 months for 2 years. The questionnaire is composed of 3 parts:
- Exposure to COVID-19
- PHQ-9 (mood assessment)
- GAD-10(anxiety assessment)

Optional Questionnaires
There are 5 bundles of optional questionnaires which participants can complete in their own time, within 24 months of registration. Participants can save their questionnaires as they complete them and return to finish them at their convenience. There will be a progress bar so the participant can see how much is left to complete. Participants will receive up to 4 reminder emails per each of the 5 batteries of questionnaires (therefore up to 20 reminders over 24 months may be given, if needed, which equates to one reminder a month).

4. Data security and privacy
Data collected at the study website, and Electronic Health Records data will be stored (EHRs). Explicit consent will be obtained from participants, and all participants will be informed of the minimal risk of identification.

To ensure privacy, all personally identifiable information will be stored separately from other data collected. This includes removing personally identifiable data from EHRs. All other information will be pseudonymised. No personally identifiable data will be shared in any publication.

To ensure security of the data, all personally identifiable data will be stored on an encrypted SDHS Web Hosting Service which is hosted in the Clinical School Computing Service data centre at the University of Cambridge and can only be viewed through restricted Safe Haven access. The database is encrypted at rest and is limited via the internal firewalls to the SDHS web server and the SDHS secure network. All other data including genetic data will be stored on secure servers such as at the University of Cambridge, Gurdon Institute, or Wellcome Sanger Institute.

5.Electronic Health Record Linkage.
This study involves linking to EHRs. All participants will be provided detailed information about what this entails and why this is required, and will be asked to consent to linkage with their electronic health record within the NHS. This will be detailed within the participant information sheet and consent form. This process will be managed in line with requirements from the national digital guidance bodies and following application to each national body, NHS Digital (England), SAIL (Wales), eDRIS (Scotland), HSCNI (Northern Ireland).

6. Data sharing
Pseudonymised data and summary statistics may be shared with academic and commercial collaborators. For all collaborators, data will be shared using specific data-sharing portals such as the European Genome-phenome Archive (EGA). Collaborators will need to obtain ethical approval, and submit an application to the research team. The application will be reviewed, and only applications in line with the aims of the study will be approved. No personally identifiable data will be shared with any collaborators. Some participants may be reluctant to share their data with commercial collaborators. Sharing participant data with commercial partners is optional. Participants do not have to consent to this. Only data from participants who do consent to this will be shared with commercial collaborators. This is described in the participant information sheet.

7. Incidental findings, mis-attributed parentage, and feedback of genetic results
DNA analysis may identify: 1. Genetic variants associated with autism; 2. Genetic variants associated with other conditions (e.g., specific types of cancer); 3. Mis-attributed parentage. As this is a research study, none of these

findings will be of clinical standard. Further, we do not have a genetic counsellor or a clinical geneticist on our team who can provide this information appropriately to participants minimizing distress. To this end, we will not be providing feedback on any of these to the participants.

## 3. PURPOSE AND DESIGN OF THE RESEARCH

**A7. Select the appropriate methodology description for this research.** *Please tick all that apply*:

- ☐ Case series/ case note review
- ☑ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☑ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☑ Questionnaire, interview or observation study
- ☐ Randomised controlled trial
- ☐ Other (please specify)

**A10. What is the principal research question/objective?** *Please put this in language comprehensible to a lay person.*

Spectrum 10K is a re-contactable resource that will allow us to identify biological and environmental factors that contribute to autism, co-occurring conditions, and wellbeing of autistic individuals. The core objectives of this project are:

1. To identify genetic predictors of autism and traits related to autism.
This will look at the whole genome and search for genetic variants that are different between autistic individuals and non-autistic individuals.
2. To identify genetic and environmental causes of co-occurring conditions in autistic people;
3. To understand gene-environment interactions that contribute to wellbeing in autistic individuals.

**A11. What are the secondary research questions/objectives if applicable?** *Please put this in language comprehensible to a lay person.*

To explore the potential of genetic scores to predict co-occurring conditions(e.g. epilepsy, depression or gastrointestinal tract issues), and long-term outcomes.

To explore environmental factors that contribute to wellbeing in autistic individuals and explore the interaction between genetics and environment.

To develop the largest autism re-contactable resource in the UK which will include data from mental health measures, and genetic data from 10,000 participants.

**A12. What is the scientific justification for the research?** *Please put this in language comprehensible to a lay person.*

Autism is highly heritable, with twin and family-based heritability estimates between 64-92%. Autism is a neurodevelopmental condition with a marked sex-difference (3:1, male to female ratio), and high mental and physical health co-morbidities. Autism has a prevalence of around 1 to 2%, with approximately 700,000 people on the autism spectrum in the UK. 70% of autistic individuals have co-occurring epilepsy, anxiety, depression, or learning disability.

These and other difficulties result in a 2.5-fold increased odds of mortality or 18 years of reduced life-expectancy. 35% of autistic individuals report planned or attempted suicide, and 85% are not in full-time employment. In the UK alone, the cost of supporting autistic individuals is £32 billion annually, which is more than cardiovascular disease, stroke, and cancer combined, making it the most costly medical condition in the UK. In contrast, research funding for autism and learning disability combined is £4 million per year in the UK compared to £521 million for cancer. There is an urgent need to both evaluate interventions to improve clinical and quality of life outcomes, and to better understand the biology of autism to improve detection, diagnosis and precision interventions, based on gene discovery and well-defined sub-grouping. This study aims to accelerate our knowledge of the biology of autism. Given the high heritability of autism, it is pertinent to understand how genetics contribute to autism and co-occurring conditions, and interact with the environment to contribute to suicidality, wellbeing, and life-satisfaction.

We argue there are five outstanding challenges to understand the genetics of autism: (a) We need larger sample sizes to robustly identify genetic variants associated with autism; (b) We need to systematically integrate functional information from developing and adult neural tissues and cell types to identify causal variants and prioritize functional genes for further analysis; (c) We need well-powered polygenic scores to integrate genetic data into diagnosis and to better understand developmental, neural, and gene-environment effects in autism; (d) We need to disentangle the underlying genetic heterogeneity in autism including better understanding co-occurring conditions; (e) We need to identify modifiable risk factors for poor wellbeing, suicidality and distress in autism.
To address these challenges, we will recruit 10,000 autistic individuals, and where possible their families (up to 40,000), to establish a UK-wide autism resource, and use previously genotyped controls from the UK Biobank. We will genotype all autistic individuals.

In addition, we will link their genetic data to self- and care-giver report phenotypic data collected during the project as well as Electronic Health Records (EHRs), where possible. Whilst large-scale genetic studies of autism exist in the world (e.g. iPSYCH in Denmark and SPARK in the United States), this study is unique in that it will be the world's largest re-contactable cohort of autistic individuals with both links to EHRs, and deep phenotypic information. The combination of deep phenotypic information, EHRs, and genetic data will provide a rich resource for understanding heterogeneity, wellbeing, and co-occurring conditions within the spectrum of autism.

**A13. Please summarise your design and methodology.** *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The Spectrum 10K study is a re-contactable cohort, where at least 10,000 autistic participants and their family members will be recruited to provide a saliva sample and complete questionnaires. Spectrum 10K aims to understand environmental factors that contribute to wellbeing in autistic individuals and explore the interaction between genetics and environment. Various aspects will be explored, including recent exposure to COVID-19. The first objective of the study is a genome-wide associated study (GWAS) (see A10) of autistic traits which will conduct a multi-trait GWAS of autism and autistic traits, with the aim of understanding the underlying biology of autistic traits and investigate how autistic traits in the typical population are related to autism. Enrolled participants and a group of non-autistic participants sourced from other cohorts like the UK BioBank will be used as comparisons. Participants' data will be linked to their electronic medical records (EHRs). This will help us better identify genetic and environmental factors, that contribute to co-occurring health conditions in autism.

Participant Identification:
Participants will register for the study at the Spectrum 10K website (www.spectrum10K.org). The website will be advertised via a national PR campaign, social media, schools, autism services and relevant charities. Participants will also be identified via primary and secondary care NHS sites. The inclusion of participants with reduced capacity will be supported & facilitated.

Registration:
Registration will consist of reading through the Participant Information Sheet, providing consent and demographic information, filling out the baseline questionnaire, completing an optional Coronavirus questionnaire and providing a saliva sample.

Participants who have been directed to the Spectrum 10K study website either by their clinician or through social media will be able to register immediately.
On the website, participants will be asked to choose which of the following categories applies to them:
- Autistic adult (> 16 years of age)
- Parent of autistic child
- Caregiver/relative/legal guardian of autistic adult with Intellectual Disability or an individual with intellectual disability who is a relative of a participating autistic individual

Relatives (up to third-degree) can only be invited by primary participants (autistic individuals enrolled in Spectrum

10K). They will receive an URL link to register and complete their own registration. Parents will be able to register their children (autistic or not) using the same user account.

Based on this information, participants will be directed to the relevant Participant Information Sheet. An adapted Participant Information Sheet will be provided for individuals with intellectual disabilities or reduced capacity. Participants will be encouraged to contact the Spectrum 10K team should they have any questions. Participants can then decide if they wish to participate in Spectrum 10K.

For participants with reduced capacity and who are above 16 years of age, consent will be obtained from a consultee. This will be achieved by assessing capacity using the British Medical Association "Assessing Mental Capacity Tool". The tool will ask a series of questions which will document whether a consultee is required. If a consultee is required, they will be asked to assent on behalf of the participant's best interests. Prior to consent, the consultee will be asked to indicate their relationship to the participant. Paid caregivers who are independent of the study will be allowed to proceed as a consultee.

Informed consent will be provided by a parent or legal guardian for all individuals less than 16 years of age. If a child turns 16 during the course of the study, parents/caregivers will be contacted to request that they invite their child to provide consent to continue as a participant in the study. If that child does not have capacity, the parent/caregiver will be invited to become a consultee for their adult child. Reduced capacity of 16-year-olds will also be confirmed using the British Medical Association "Assessing Mental Capacity Tool".

Participants will complete the relevant consent form online.

Once participants have provided consent they will be asked to provide their name, date of birth, email address, NHS number, GP details, diagnostic information and demographic details. Parents of autistic children aged below 16 will be asked to register their own contact details, followed by the details of the child(ren) to be enrolled in the study.

Collection of questionnaire and genetic data:
Each participant will be assigned a unique study ID number.
Participants will complete a mandatory sign-up baseline questionnaire (described in detail in later sections). Participants will also have the opportunity to complete an optional questionnaire about COVID-19. If selected, the participant will be asked to complete the questionnaire every 3 months for a period of 2 years. Additional optional questionnaires will be available after the sign-up questionnaire is complete. These can be completed in the participants own time over a period of 24 months or immediately if the participant chooses. Participants will be asked to provide a saliva sample, and will be sent a saliva collection DNA kit by post which they can return via freepost.

Verification of professional diagnosis of autism:
Once participants have provided consent, they will be asked, where possible, to provide an electronic copy of their report confirming their autism diagnosis. This can be uploaded as an electronic copy, a scanned copy of the original document or as a picture, as long as it is legible. However, this is not mandatory. This will enable comparison of the genetics and other phenotypic measures between the autism group with a verified autism diagnosis and those without a verified autism diagnosis, family members, and individuals from the general population. Participants who are not yet formally diagnosed (self-diagnosed) will not be eligible to participate. Self-diagnosed individuals will be invited to register at the Cambridge Autism Research Database (CARD) (Approved by the University of Cambridge Psychology Research Ethics Committee: PREC.2017.056) to hear about other studies taking place at the Autism Research Centre. Participants have the opportunity to update their autism diagnosis on CARD, should they receive a diagnosis during the course of the Spectrum 10K study. If this happens and they become eligible to participate and recruitment is ongoing, we will direct them to the Spectrum 10K website. CARD does not currently recruit participants with reduced capacity.

Additional questionnaires:
After registration, participants will then have access to complete the optional questionnaires. The phenotypic questionnaires will capture the following areas over 5 phased batteries of questionnaires:
- Autistic Traits, Repetitive Behaviour and Sensory Input
- Depression, Anxiety, ADHD and OCD.
- Vulnerability, Camouflaging and Resilience
- Quality of Life, Systemizing, Empathy and IQ.
- Mentalising, Short-term memory.
- Development (only for children).

Follow up contact:
If participants have completed the COVID-19 questionnaire at baseline, they will receive a reminder every 3 months to repeat the questionnaire for a period of two years. The questionnaire will ask about whether a participant was unwell due to COVID-19 or knew a person who was, symptoms they experienced, treatment management and shielding. It will also ask about the impact of COVID-19 on their finances, mood and anxiety levels. This will help us to understand

the impact of COVID-19 on the autism community. Participants will receive a maximum of 4 reminders to complete additional questionnaires for each phase of questionnaires over a 24 month period.
Participants will also be invited to participate in other studies based on the information they provide. They will receive a maximum of 4 invitations per year. Participants who optionally consent to receive newsletters or updates about Spectrum 10K will receive newsletters twice a year. This will include information about the progress of the Spectrum 10K study. Information about related research will be made available on the ARC website (www.autismresearchcentre.com).

**A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?**

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

*Give details of involvement, or if none please justify the absence of involvement.*
We established a Patient and Public Involvement and Engagement (PPIE) Advisory Group. It is comprised of 3 autistic individuals, 3 parents of autistic children, 2 NHS clinicians and a representative from Autistica (UK's leading autism research charity). This group is representative of the various groups that may become involved in this study. It is scheduled to meet twice a year for the next 4 years.

To date, we have involved our PPIE Advisory Group with the following tasks:
Focus Group:
We held a Focus Group to present an overview of the study. Advisors were asked to give feedback about the study design and the participatory aspect. Based on their feedback, we have made amendments to study documentation and procedures. For example, we have made amendments to the registration and data collection processes, with the aim to minimise burden on participants.

Consent form and Participant Information Sheet feedback:
Advisors were asked to give feedback about the legibility and design of these documents, which we have taken into account, where appropriate.

Phenotypic Questionnaires:
Participants were asked to comment on the type of optional questionnaires that were proposed. Panel members gave suggestions on the types of questionnaires to include.

Going forward examples of how we will involve our PPIE group in Spectrum 10K includes the following:
1.Website user testing:
Asking users to complete the sign-up process of the website with a test version and getting feedback on the user interface. We will ask for feedback regarding the layout, usability and information included on the website.

2. Dissemination of findings. We will request feedback about newsletters that we intend to send to participants bi-annually.

## 4. RISKS AND ETHICAL ISSUES

### RESEARCH PARTICIPANTS

**A15. What is the sample group or cohort to be studied in this research?**

Select all that apply:

- [ ] Blood
- [ ] Cancer

- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [x] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [x] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

| | |
|---|---|
| Gender: | Male and female participants |
| Lower age limit: 0 | Years |
| Upper age limit: 150 | Years |

**A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).**

Autistic individuals must have a diagnosis of autism from a qualified professional.
Participants can include male and female participants of all ages, ethnicities, and capacities.
Eligible participants can include up to third degree biological relatives of autistic individuals who are participants in Spectrum 10K (regardless of autism diagnosis and reduced capacity).
All participants must be living in the UK at the time of recruitment.

**A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).**

Participant is unwilling to provide consent;
Participant has not received an autism diagnosis from a qualified professional (i.e. who is therefore self-diagnosed) or is not related to an autistic individual who is participating in the study.
Participant has lack of capacity to consent who does not have someone who can act as a consultee.
Participant is not living within the UK.

## RESEARCH PROCEDURES, RISKS AND BENEFITS

**A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol.** *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

| Intervention or procedure | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Information provision (advertisement or clinician) | 1 | 0 | 5 minutes | Advertising company, social media, GP practice, or clinician involved in care |
| Website Registration | 1 | 0 | 10 | Self Directed or with research staff if appropriate. |
| Reading Participant Information Sheet & Providing consent | 1 | 0 | 20 minutes | Self directed in online setting or with research staff if appropriate. |
| Mandatory Questionnaire - Baseline Questionnaire | 1 | 0 | 20 - 30 minutes | Self-collection |
| Saliva sampling | 1 | 0 | 20-60 minutes | Self-collection<br>Participants will be posted a kit(s) so the sample collection can be completed at home. Sample(s) are returned in the post using a freepost envelope |
| Additional Optional Questionnaires | 7 | 0 | 20 - 30 mins | Self-collection. |
| Optional COVID-19 Questionnaire | 8 | 0 | 20-30 minutes | Self-collection. |

**A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol.** *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

| Intervention or procedure | 1 | 2 | 3 | 4 |
|---|---|---|---|---|

**A21. How long do you expect each participant to be in the study in total?**

Spectrum 10K is a re-contactable resource. The initial enrolment and sample collection phase of the research will be completed within approximately 2 weeks for each participant. They will still be active through completion of the non-mandatory questionnaires over a 24 month period. The Spectrum 10K study team will also contact participants up to 4 times per year to participate in other studies. A participant is deemed to have exited the study if they choose to withdraw. Participants are free to withdraw participation at any time. Participation in future studies will be dependent on each study specific requirements and ethics.

**A22. What are the potential risks and burdens for research participants and how will you minimise them?**

*For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes*

*to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.*

Recruiting vulnerable participants
The cohort recruited will include autistic adults and participants with reduced capacity. Measures have been put in place to ensure participants feel safe, well informed and free to ask any questions they need. All the lead investigators named in this application are international experts in the field of autism or have a wealth of experience in collecting genetic data from patients being treated for psychiatric disorders and debilitating conditions. Useful links and phone numbers of relevant charities such as the National Autistic Society helpline will be provided throughout the website. Participants will also be able to contact the recruitment team with any queries at the Autism Research Centre.

Saliva sample provision.
DNA will be collected using saliva samples. All participants will be asked to provide a saliva sample. All saliva sample kits will include an illustrated leaflet providing concise instructions for using the saliva kit and how to return to the laboratory in a pre-stamped addressed envelope. Participants will have the option to request assisted DNA collection kits. These kits provide alternate means of collecting DNA that participants may find easier to use (from ISOHELIX limited). Assisted kits include foam swabs which can be used to collect saliva. This option may be useful for participants with intellectual disabilities and for young children.

Questionnaire completion.
All participants will be asked to complete 1 mandatory baseline questionnaire and 1 COVID-19 questionnaire (optional). The mandatory baseline questionnaire will have two parts:
- AQ-10 (Autism Spectrum Quotient, 10 item version)
- Developmental and Medical History Questionnaire.

The COVID-19 Questionnaire(optional) will be repeated every 3 months over 2 years if selected and will have 3 parts:
- Disease exposure questionnaire.
- PHQ-9 (Mood assessment)
- GAD-10(Anxiety assessment)

Secondary Questionnaires (optional)
Participants can also choose to complete optional additional phenotypic questionnaires. Information will be provided explaining why we have selected these questionnaires. Questionnaires will be provided in 5 phases to ensure participants do not feel overwhelmed. Questionnaires can be completed all at once, or over a time period of 24 months. Users can save their work at any point an come back to complete at their convenience. The website will allow a user to see their progress clearly. Reminder emails will be sent to all participants.

It is possible that members will feel that providing a saliva sample and having to complete questionnaires is an additional burden they do not wish to undertake. We will make it very clear that patients are under no obligation to take part and that any future needs and rights they have will not be affected by their participation (or lack of).

Security and privacy.
There is minimal risk that participants will be identified. All personally identifiable information will be stored separately from other data including EHRs and genetic data. Personally identifiable information will be stored on the University Safe Havens. Other data will be pseudonymised and stored on secure servers such as that at the University of Cambridge, Sanger Institute or Gurdon Institute. EHRs will remove any personally identifiable information. Only anonymised data will be shared with collaborators. Further details about data security is outlined in the protocol and other sections.

**A24. What is the potential for benefit to research participants?**

There are no direct benefits to participating in this study. However, this study will help to further understanding about autism. This research may lead to better intervention and diagnostic guidelines and improve future care and support for autistic individuals.

## RECRUITMENT AND INFORMED CONSENT

***In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.***

**A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources**

**will be used?***For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Participants will be identified via:
- PR Campaign/Social Media/Advertising
- NHS Secondary care and tertiary care sites
- NHS Primary Care GP practices.

PR Campaign:
A media company - Four Health Communications has been employed to promote Spectrum 10K. This is a specialised communications agency with expertise in patient services and healthcare clients. Participants recruited will be individuals who have responded to public advertisement, newspaper articles, letters to schools, emails to databases, or notices on social media (Facebook, Twitter).

NHS Secondary and Tertiary Care sites:
Hospital and community based sites throughout the UK will identify and recruit study participants. Participants will be identified by speaking to clinicians or direct care/allied health professionals who are delegated to perform the research study at that location. Participants will be supported through study registration, consent, questionnaire completion and saliva sample provision.

NHS Primary Care GP practices:
Participating GP practices will identify participants via coded patient registers. This will be performed by the GP practice and the list screened for patients for whom it would be inappropriate to contact. An invitation letter will be sent to participants informing them about the study and inviting them to take part. Participants will sign up to the study and access the study website from their own home.

**A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?**

◉ Yes ○ No

*Please give details below:*
Identification of potential participants at Primary, Secondary and Tertiary care sites will involve the screening of clinic lists or identification of participants in clinics. These activities will only be performed by members of the the direct care clinical team who are delegated to work on the Spectrum 10K study.

**A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.***Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Hospital medical records, clinic lists and GP registers will be reviewed by the direct care team. Any identification of participants will be in line with the specific Trust Data Protection policy and General Data Protection Regulations.

**A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?**

○ Yes ◉ No

**A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?**

◉ Yes ○ No

*If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).*

PR Campaign:
A media company - Four Health Communications has been employed to advertise the project on our behalf. This is a specialised communications agency with expertise in patient services and healthcare clients. Participants

recruited will be individuals who have responded to public advertisement, newspaper articles or notices on social media (Facebook, Twitter).

Posters and Leaflets:
Ethically approved leaflets and posters will be supplied to schools, GP practices and Secondary care sites.

Emails:
Autism databases, schools, and charities will be emailed.

**A29. How and by whom will potential participants first be approached?**

Participants will be approached either by a member of their direct care clinical team, receive a letter/email/poster from their GP/school/research database/charity informing them about the study, or will see a study advertisement/article/social media material informing the participant about the study.

**A30-1. Will you obtain informed consent from or on behalf of research participants?**

◉ Yes ○ No

*If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.*

*If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.*

All participants will provide consent online. In line with MHRA guidance on seeking consent by electronic methods, for research that is not a CTIMP, an electronic signature will be requested. Participants will read through a number of consent items and will indicate their agreement to these consent items through an explicit consent statement to which they can consent to in a yes/no format.

All participants with capacity and who are above 16 years of age will provide informed consent to participate in Spectrum 10K. The participant information sheet will provide details about the consent process, and exactly what the participants will be consenting to. For all individuals less than 16 years of age, informed consent will be obtained from a parent or legal guardian. Parents will be provided with dedicated participant information sheets and consent forms.

In line with the Mental Capacity Act 2005 and Adults with Incapacity (Scotland) Act 2000, for participants with reduced capacity (who are autistic individuals or relatives of a participating autistic individual), participants will be provided with an adapted easy-to-read participant information sheet, and a consultee will be identified who will be asked to assent for the participant, if appropriate.

Capacity to consent will first be assessed by asking a relative/legal guardian/clinician to complete the British Medical Association "Assessing mental capacity tool". This will ask a series of questions which will determine if a consultee is required. If it is determined that a consultee is required, they will be asked to indicate their relationship to the participant. The consultee will be directed to the Consultee Participant Information Sheet and Consultee Declaration Form to indicate consent. If at any time the consultee advises that in their opinion the wishes of the participant indicate that they would not wish to take part or they have changed their mind about participating, then it will be noted as declined consent or withdrawal if they have previously enrolled.

*If you are not obtaining consent, please explain why not.*

*Please enclose a copy of the information sheet(s) and consent form(s).*

**A30-2. Will you record informed consent (or advice from consultees) in writing?**

○ Yes ◉ No

*If No, how will it be recorded?*

In line with the Mental Capacity Act 2005 and joint guidance on e-consent by MHRA and HRA the consent process will be documented on the website as follows:
Capacity to consent will first be assessed by asking a relative/legal guardian/clinician to complete the British

Medical Association "Assessing mental capacity tool". This will ask a series of questions which will determine if a consultee is required. If it is determined that a consultee is required, they will be asked to indicate their relationship to the participant. The consultee will be directed to the Consultee Participant Information Sheet and Consultee Declaration Form to indicate consent.

Consultees will read through a number of consent items and will indicate their agreement to these consent items through an explicit consent statement to which they can consent to in a yes/no format. A copy will be available to download and save for their records. This will be time stamped and dated.

The study team will be available by phone to answer any questions during this time

**A31. How long will you allow potential participants to decide whether or not to take part?**

As participants are required to register and consent online, participants can take as long as they want to decide to participate. If recruited in person, for instance, at an NHS secondary site, a participant will be given at least 24 hours to consider participation.

**A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?**

- ○ Yes
- ○ No
- ◉ Not Known

*If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?*

It is possible that participants signing up to the current project may have been involved in other research projects. We will advertise our study to participants registered at the Cambridge Autism Research Database and other autism research databases. Participating in other research projects will not affect participation in Spectrum 10K.

**A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?***(e.g. translation, use of interpreters)*

The study website and all study documentation is provided in English only. Due to the large scale of the study we are not able to provide a translation service. However, for participants identified through NHS secondary care sites, NHS translation services can provide support to sign up and involvement. We have also developed easy read version of the information sheet and some questionnaires.

**A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?**

The study website and all study documentation is provided in English only.

**A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study?** *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.
- ◉ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

*Further details:*

It is not practicable for the research team to monitor capacity due to:

The large number of study participants(10,000+)

The majority of participants will register, consent and participate online from their home. It is not possible in this setting to monitor capacity.

At NHS sites and online, study participation does not include any additional follow- up visits where changes in capacity can be assessed.

## CONFIDENTIALITY

**In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.**

### Storage and use of personal data during the study

**A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?** *(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [ ] Electronic transfer by magnetic or optical media, email or computer networks
- [ ] Sharing of personal data with other organisations
- [ ] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [ ] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

*Further details:*
Data collected via the Spectrum 10K website will be defined as source data. This includes all the information collected at registration, the baseline questionnaires, and all optional questionnaires. Where participants register with the study via an NHS clinic (in person), or need assistance with a member of staff, staff will access the online platform at the hospital clinic and support the participant through the online registration and consent process. The study team will be available by phone to answer any questions during this time. The data will be automatically captured at the time of registration/questionnaire completion. Identifiable information (including but not limited to name, age, address, email, phone number, medical diagnosis, name of the GP, NHS number) will be stored on the Clinical School of Medicine Secure Data Hosting Service (SDHS). All participant data will be registered with a unique study ID.

Genetic data
Genetic data will include data generated from the analysis of the DNA extracted from saliva samples. Examples of these type of data includes genotype data and exome sequencing data.

Linked data
Linked data refers to official records collected from other institutions such as the NHS and GP clinics. Consent will be obtained from all participants at registration to collect linked data.

Spectrum 10K will collect information on health record linked data. These are collected by the NHS and GP practices. These records will contain information on visits to doctors and hospitals, details of community care, mental health, eye tests, hearing and dental records.

Generated data
These are data generated from analyses of collected Spectrum 10K data from one or more variables. Examples of these types of data include derivation of Body Mass Index (BMI) from height and weight, and Deprivation Indices from postal codes.

Data Storage and Security
Source, linked and generated data: Source, linked, and generated data will be stored at the University of Cambridge's Clinical School of Medicine SHDS. The SHDS website publishing system is currently under development and should be ready for the launch of the Spectrum 10K study. If it is not ready in time, the existing web hosting architecture, CSCS Secure Azure database service, will be used until the system can be transferred fully into the SDHS Web Hosting service.

The SDHS Website Hosting service is hosted in the Clinical School of Computing data centre. The database is encrypted at rest and access is limited via internal firewalls to the SDHS web server and the SDHS secure network.

The CSCS Secure Azure database service uses the Azure Cloud platform to host an encrypted at-rest database which is limited to access via a secure firewall to the SDHS web server and the SDHS secure network.

Identifiable information such as name, date of birth and contact details, and free text boxes from linked data will be stored in one database, with each person having a unique participant ID. Other source data will be stored with the participant ID only, in a separate database. All source data will be shared with researchers without any identifiable information and using only the participant ID.

Genetic data
Genetic data will be stored on servers such as the University of Cambridge or Wellcome Sanger Institute Servers or the European Genome-Phenome Archive (EGA). Only data on the EGA will be made available to approved researchers.

**A37. Please describe the physical security arrangements for storage of personal data during the study?**

Source, linked and generated data will be stored at the University of Cambridge's Clinical School of Medicine Secure Data Hosting Service. The database is encrypted at rest and access is limited via internal firewalls to the SDHS web server and the SDHS secure network.

The existing web hosting architecture, CSCS Secure Azure database service, will be used until the system can be transferred fully into the SDHS Web hosting service. The CSCS Secure Azure database service uses the Azure Cloud platform to host an encrypted at-rest database which is limited to access via a secure firewall to the SDHS web server and the SDHS secure network.

**A38. How will you ensure the confidentiality of personal data?***Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

Identifiable information (including but not limited to name, age, address, email, medical diagnosis, name of GP, NHS number) will be stored on the SDHS Web Hosting Service in the Clinical School of Computing data centre in the Univerisity of Cambridge. All participant data will be registered with an individual study ID, which will pseudonymise any data collected.

Identifiable information such as name, date of birth and contact details will be stored in one database, with each person having a unique participant ID. Other source data will be stored with the participant ID only in a separate database. All source data will be shared with researchers without any identifiable information and using only the participant ID.

If a participant has withdrawn from the study, they will be asked to stipulate how they would like their data to be stored. Three options will be provided:

No Further Contact:
This means that Spectrum 10K would no longer contact the participant directly but would have permission to retain and use information and samples provided previously and to obtain and use further information from health records.

No Further Access:
This means that Spectrum10K would no longer contact a participant or obtain further information from health records in the future, but still has permission to use the information and samples provided previously.

No Further Use:
In addition to no longer contacting a participant or obtaining further information, any information and samples collected previously would no longer be available to researchers. Spectrum 10K would destroy samples (although it may not be possible to trace all distributed sample remnants) and would only hold information for archival audit purposes. Such a withdrawal would prevent information about the participant from contributing to further research, but it would not be possible to remove data from research that had already taken place.

**A40. Who will have access to participants' personal data during the study?** *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

In addition to the direct research team, some personally identifiable information will be shared with national bodies to collect EHRs (e.g. Name, address, date of birth, gender, and NHS number). The Spectrum 10K study will seek permission to view the electronic health records (EHR) of participants. This will be performed following participant consent and application to the national bodies who hold and maintain medical records: NHS Digital (England), SAIL databank (Wales), eDRIS (Scotland) and HSCNI (Northern Ireland). A participants NHS number, DOB, name, gender and postcode will be used to identify their medical records and data from these records will be shared back with the research team. This data will be held against a unique study number and with all personal identifying information removed (pseudonymised).

## Storage and use of data after the end of the study

**A41. Where will the data generated by the study be analysed and by whom?**

The data generated will be analysed by members of the research team and co-investigators on Spectrum 10K , under the supervision of [redacted]. Where patients have explicitly given consent for their data to be used by the research team, this will be undertaken on university computers, all of which are password protected. All data will be used in an anonymised linked format and no personal details will ever be included in these datasets.

**A42. Who will have control of and act as the custodian for the data generated by the study?**

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | | [redacted] |
| Post | Director | Autism Research Centre. | |
| Qualifications | FBA FMedSci | | |
| Work Address | 18B Douglas House | | |
| | Trumpington Road | | |
| | Cambridge | | |
| Post Code | CB2 8AH | | |
| Work Email | [redacted] | | |
| Work Telephone | [redacted] | | |
| Fax | | | |

**A43. How long will personal data be stored or accessed after the study has ended?**

◯ Less than 3 months

○ 3 – 6 months

○ 6 – 12 months

○ 12 months – 3 years

◉ Over 3 years

*If longer than 12 months, please justify:*
The Spectrum 10K study will act as a recontactable resource. Participants will consent to the long-term storage of identifiable and non-identifiable information. All participants will be consented to long-term storage.

**A44. For how long will you store research data generated by the study?**

Years: 25
Months:

**A45. Please give details of the long term arrangements for storage of research data after the study has ended.***Say where data will be stored, who will have access and the arrangements to ensure security.*

Source, linked and generated data will be stored at the University of Cambridge's Clinical School of Medicine SHDS. All data collected will only be accessible by approved researchers from the Spectrum 10K study.

Genetic data will be stored on servers such as the University of Cambridge or Wellcome Sanger Institute Servers or the European Genome-Phenome Archive (EGA). Data on the EGA will only be made available to approved researchers. Authorised researchers will be external researchers who apply and have been granted access to parts or all of the data.

If a participant has withdrawn from the study, they will be asked to stipulate how they would like their data to be stored. Three options will be provided:

No Further Contact:
This means that Spectrum 10K would no longer contact the participant directly but would have permission to retain and use information and samples provided previously and to obtain and use further information from health records.

No Further Access:
This means that Spectrum10K would no longer contact a participant or obtain further information from health records in the future, but still has permission to use the information and samples provided previously.

No Further Use:
In addition to no longer contacting a participant or obtaining further information, any information and samples collected previously would no longer be available to researchers. Spectrum 10K would destroy samples (although it may not be possible to trace all distributed sample remnants) and would only hold information for archival audit purposes. Such a withdrawal would prevent information about the participant from contributing to further research, but it would not be possible to remove data from research that had already taken place.

## INCENTIVES AND PAYMENTS

**A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?**

○ Yes ◉ No

**A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?**

○ Yes ◉ No

**A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?**

○ Yes ◉ No

## NOTIFICATION OF OTHER PROFESSIONALS

**A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?**

○ Yes ◉ No

*If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.*

## PUBLICATION AND DISSEMINATION

**A50. Will the research be registered on a public database?**

*The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.*

○ Yes ◉ No

*Please give details, or justify if not registering the research.*
Some research may be pre-registered, but as this is not a clinical trial, research will not be registered in specific databases.

*Please ensure that you have entered registry reference number(s) in question A5-1.*

**A51. How do you intend to report and disseminate the results of the study?***Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☑ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

**A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?**

All study data will be linked to an individual study ID which will protect participants' personal information. Only pseudonymized data will be shared with collaborators.

**A53. Will you inform participants of the results?**

(●) Yes ( ) No

*Please give details of how you will inform participants or justify if not doing so.*
The Spectrum 10K study will distribute a biannual newsletter to publicise research findings and any updates about the study (e.g. and other research studies taking place at the ARC). The Spectrum 10K study website and Spectrum 10K social media accounts will also be a valuable platform for disseminating results through online updates. However, we will not provide individual feedback on results including genetic results.

## 5. Scientific and Statistical Review

**A54. How has the scientific quality of the research been assessed?***Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

*Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:*
The scientific quality has been reviewed by the following:

1. Four independent reviewers during the grant application process to the Wellcome Trust (who ultimately awarded the grant).

2. Two independent reviewers from the Department of Psychiatry at the University of Cambridge, who reviewed the application prior to submission to the Wellcome Trust.

3. An independent external peer review of the study protocol has been performed by Cambridgeshire and Peterborough NHS Foundation Trust and the University of Cambridge.

*For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.*

*For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.*

**A56. How have the statistical aspects of the research been reviewed?***Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

*In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.*

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | [redacted] | [redacted] |

| | |
|---|---|
| Department | Human Genetics |
| Institution | Wellcome Trust Sanger Institute |
| Work Address | Wellcome Genome Campus |
| | Hinxton |
| | Cambridgeshire |
| Post Code | CB10 1SA |
| Telephone | |
| Fax | |
| Mobile | |
| E-mail | [redacted] |

*Please enclose a copy of any available comments or reports from a statistician.*

**A57. What is the primary outcome measure for the study?**

The primary outcome of this study is to understand the underlying biology of autism and its interaction with environmental factors. We hope that this new knowledge that will lead to improvements in autism, co-occuring conditions, and wellbeing of autistic individuals. We will assess this outcome using genetic results as well as assessing phenotypic data, electronic medical health records and other information participants will provide.

**A58. What are the secondary outcome measures?***(if any)*

N/A

**A59. What is the sample size for the research?** *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 40000

Total international sample size (including UK):

Total in European Economic Area:

*Further details:*
The total sample size of 40,000 will consist of at least 10,000 autistic participants and a maximum of 30,000 first, second and third-degree relatives. In cases of complex families where there are three or more autistic individuals within the larger families, we will endeavour to collect as many individuals within the family to study these families in detail. It is likely that these data will be used in conjunction with datasets for which data collection is currently being planned. This field is moving rapidly and the combination of individually large datasets combined to form larger sample sizes will provide additional power.

**A60. How was the sample size decided upon?** *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Power calculations were conducted for the primary, immediate end-point: A GWAS of autism.

Power calculations for the GWAS analyses were conducted using Genetic Power Calculator126. The primary autism GWAS will have 80% power to detect a variant with Odds Ratio = 1.04. The autistic traits GWAS will have 80% power to detect a variant with a variance explained (R2) of 0.01% roughly corresponds to an odds ratio of 1.02 for common variants (minor allele frequency > 0.05). For polygenic scores, power calculations were conducted in line with the theory laid out elsewhere. Statistical power graph for polygenic score regression analysis is dependent on the heritability of the testing and the training phenotypes, and the genetic correlations between the two phenotypes, which is equivalent to the square root of the variance explained (R2) by polygenic scores in an infinitely large sample. Phenotype 2 represents one of the various testing phenotypes (developmental trajectories, imaging metrics etc). Power calculations have been conducted separately for the autism and the autistic traits GWAS. At a SNP heritability > 0.15 for the autistic traits GWAS, the Lifelines cohort will have sufficient statistical power to detect an effect that’s

equivalent to rg > 0.3 between the two phenotypes in an infinitely large sample. Power calculations for investigating the combined contribution of common and rare variants were conducted using G*Power (http://www.gpower.hhu.de/). At a sample size of 3,000, the study will have 80% power to significantly (P < 0.05) identify a predictor that explains 0.25% of the variance (R2 = 0.0025). Using the entire SPARK and MSSNG dataset (N = 5,000), the study will have 80% power to detect PTV-scores that explain 0.15% of the total variance in the phenotype. At an N ~ 30,000, the study will have 80% power to identify a predictor that explains 0.025% of the variance. Power calculations were done using pilot analysis in the Simon's Simplex Collection (N = 2,221), using a linear regression.
We estimate the case-control GWAS will identify between 155-165 new loci. This estimate was arrived at using two methods. In the first method, we calculated the slope of the loci discovered to the total number of autism cases included in the GWAS using existing GWAS. Extrapolating it to N = 100,000 cases yielded 165 new loci. This follows from observations from other GWAS studies that there is a largely linear relationship between sample size and loci identified in GWAS. In the second method128, we accounted for population prevalence of autism under the hypothesis that cases in rarer conditions will have a greater liability, and thus, will have a greater difference in liabilities between cases and unselected controls. Using a population prevalence of 1% for autism, 100,000 cases and twice as many controls, we estimate that the study will discover 155 new loci.

**A61. Will participants be allocated to groups at random?**

○ Yes ◉ No

**A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.**

Primary statistical analyses
We will conduct two complementary GWAS analysis: GWAS of autism (case-control GWAS) and GWAS of autistic traits. We estimate a final sample size of 100,000 cases and a roughly equal number of controls for the case-control GWAS. All cases from the UK will be genotyped in the UK Biobank Axiom array to enable the use of participants in the UK Biobank as population controls. In this phase of the study, we will not genotype parents, but will bank their DNA for future analyses. For both the GWAS, we will conduct common and low-frequency variant GWAS by combining data from multiple different cohorts. In all cohorts, imputation will be conducted using data from the 1,000 Genomes, the Haplotype Reference Consortium, or the UK-10K reference panel. If data becomes available from larger consortium (e.g. TOPMED, and 100,000 Genomes Project), we will use these panels for imputation. Data will be quality controlled for allele frequency, Hardy Weinberg equilibrium, per SNP and per-individual genotyping rate, and imputation accuracy. Population stratification will be controlled for by including ancestry principal components as covariates or by utilizing a linear mixed-effects model. Replication-by-proxy will be conducted by investigating concordance of effect direction of the lead SNPs from one GWAS in the other GWAS, given the high twin and SNP genetic correlation between autism and autistic traits. In addition, for both GWAS we will conduct 'in sample replication' by assessing concordance of effect direction of lead SNPs in all cohorts. We will use a conservative threshold of P < 5x10-9 to account for the greater number of statistical tests conducted when investigating low-frequency variants. Statistical power calculations suggest that the final sample has 80% power to identify variants with an odds ratio = 1.04, and calculations suggest that the study will identify approximately 155-165 novel variants. Using multivariate techniques, we will meta-analyse the GWAS of autism and autistic traits, an approach that has been used for ADHD and depression to further increase sample size, identify additional variants, and increase the predictive power of polygenic scores derived from the meta-analyses.

We will conduct fine-mapping analyses to identify potential causal variants, and integrate eQTL, methylation, and Hi-C data from the adult and developing brain to prioritize genes for functional analyses. Integrating data from multiple different genomic functional categories, we will fine-map and prioritize causative variants and genes for downstream functional analysis.

We will conduct CNV association meta-analysis of autism and autistic traits. CNVs will be called from quantile normalized raw probe-set intensity values. Probabilistic CNV calls will be generated from Penn CNV90, after merging adjacent CNVs with small gaps, and removing samples with more than 200 CNVs, and had a call rate < 96%. Individual CNVs will be excluded if they are covered by <10 probes or had poor density of coverage. We will focus on rare CNVs (population allele frequency < 0.1%) based on the Database of Genomic Variation. Analyses will be conducted at a probe level after translating CNV calls and quality to a probe-level. We will include sex, genetic principle components, and age as covariates. Meta-analyses across cohorts will be conducted based on previously described procedures.

Following the primary-analysis we will conduct the following analyses:

a. To understand the neural underpinnings of the autism GWAS, we will investigate enrichment in genes highly expressed in specific human and mouse neuronal cell types, genes with specific expression in different brain tissues, and genetic pathways.
b. To understand if the autism GWAS is enriched for specific functional categories, we will investigate enrichment in genomic regions defined by functional properties (e.g. open chromatin regions, conserved regions, genes intolerant to loss-of-function mutations, transcriptionally dysregulated genes in autism).
c. To understand the shared genetics between autism and other phenotypes, we will conduct genetic correlation analyses at both a global and local genomic level, using phenotypes from the UK Biobank and other large GWAS. We will use Structural Equation Modelling using summary GWAS data to further delineate the effect of mediator phenotypes on autism. To identify shared loci between autism and other neuropsychiatric conditions, we will conduct Bayesian co-localization analyses.
d. To identify modifiable risk factors for autism and other co-morbid conditions, we will conduct two-sample summary Mendelian Randomization analyses and Latent Causal Variable analyses.
e. To identify the correlation between autism and normative development, we will investigate how polygenic scores contribute to cross-sectional and longitudinal speech, communication and motor development in Lifelines Cohort (N ~ 3000), and ALSPAC (N ~ 5000). We will further investigate the role of polygenic scores in the development of typical peer networks and social relationships in the Add Health Cohort (N ~ 4,000).
f. To investigate the indirect effects of autistic traits on adaptive behaviour and overall autism symptom severity, we will test if polygenic scores of autism in the untransmitted parental alleles are associated with scores on the Vineland Adaptive Behaviour Scale and ADOS-G120 scores in the children in the Simon's Simplex Collection (N ~ 2,500 families) and the Autism Genetic Resource Exchange (N ~ 1,500 families).
g. To understand the effects of autism on typical brain development, we will investigate the association of autism polygenic scores in cross-sectional and longitudinal structural and functional brain networks in the ABCD (N = 10,000) and the UK Autism Biobank (N = 100,000).
h. To investigate secondary medical phenotypes associated with autism, we will investigate if polygenic scores for autism (developed excluding the UK Autism Biobank) are associated with clusters of medical phenotypes identified in EHRs in the UK Autism Biobank.
i. To investigate the combined contribution of common and rare-variants with autism severity, we will investigate if polygenic scores for autism excluding the Simon's Simplex, MSSNG, and the AGRE cohorts, interact with de novo LGD variation in genes intolerant to loss-of-function mutations in the three cohorts (SSC, MSSNG, and AGRE) to modify the severity of the condition.
j. To reposition drugs in autism. First, using eQTL data, we will impute transcriptomes for the autism GWAS. This, in combination with drug-induced transcriptome, will help identify enriched drug targets. Second, we will generate 'drug pathways' by using data on drug-gene interactions, and test for enrichment of these pathways in the autism GWAS.

2.2.3 Secondary analyses:
The unprecedented sample size will also allow us to conduct several secondary GWAS analyses to investigate sources of heterogeneity (Figure 1). We will conduct the following additional analyses:

1. Sex-interaction and stratification analyses: Given the sex differences in prevalence of autism (between 3:1, males to females), it is important to investigate the sex-specific effects of common variants in autism. We will conduct a sex-interaction GWAS of both autism and autistic traits to identify loci with differential effects based on sex. As several downstream analyses are not developed for an interaction model, we will further conduct sex-stratified analyses to identify sex-specific genes, pathways, and enriched tissues, and sex-specific genetic correlations. Sex information will be available for all cohorts included in the primary analyses.

2. Social and non-social autistic traits GWAS: Several lines of research have demonstrated that social and non-social domains of autism are phenotypically and genetically dissociable. A few studies have investigated the genetic architecture of these domains in small cohorts of autistic individuals, but results have been limited by the small sample size and low statistical power. We will conduct GWAS of social and non-social domains in the autism cohorts, and, in parallel, GWAS of social and non-social autistic traits in the general population by dividing items in the AQ-10 and other autistic trait measures into those that capture social and non-social traits. We will additionally investigate if these domains are genetically dissociable using genetic correlation, if polygenic scores predict different outcomes, and enrichment in different genes, tissues, and cell types. Finally, using transcriptomic data from the developing brain, we will investigate shared and distinct enrichment of polygenic signals of the social and non-social GWAS in different spatio-temporal gene expression modules. Using EHRs we will investigate if polygenic scores from the social and non-social domains are associated with different co-morbidities. We expect domain specific information from 3 autism cohorts (N ~ 60K, Simon's Simplex, UK Autism Biobank, and AGRE), and social and non-social autistic traits information on all participants included in the autistic traits GWAS (N ~ 250K).

3. GWAS of autism subgroups: To better understand heterogeneity within the autism spectrum, we will conduct phenotypic clustering (K-means, Finite Mixture Modelling) within the autism spectrum (N > 60K - Simon's Simplex, AGRE, SPARK, and the UK Autism Biobank), and conduct GWAS of autism in the clustered cohorts. Genetic correlation analyses will be conducted to investigate if the polygenic architecture is dissimilar across the clusters. Using EHRs in the UK cohort, we will investigate if these clusters are enriched for different co-morbidities.

## 6. MANAGEMENT OF THE RESEARCH

**A63. Other key investigators/collaborators.** *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | [redacted] | [redacted] |
| Post | Head of Paediatrics | | |
| Qualifications | MD, PhD, ScD. | | |
| Employer | University of Cambridge | | |
| Work Address | Department of Paediatrics<br>Level 8, Biomedical Campus<br>Cambridge | | |
| Post Code | CB2 0QQ | | |
| Telephone | | | |
| Fax | | | |
| Mobile | | | |
| Work Email | [redacted] | | |

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | [redacted] | [redacted] |
| Post | Head of Human Genetics, Genome Mutation and Genetic Disease Group | | |
| Qualifications | | | |
| Employer | Wellcome Sanger Institute | | |
| Work Address | Wellcome Genome Campus,<br>Hinxton<br>Cambridge | | |
| Post Code | CB10 1SA | | |
| Telephone | | | |
| Fax | | | |
| Mobile | | | |
| Work Email | [redacted] | | |

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | [redacted] | [redacted] |
| Post | Group Leader, Population and medical genomics in under-studied populations | | |
| Qualifications | PhD. | | |
| Employer | Wellcome Sanger Institute | | |
| Work Address | Wellcome Genome Campus,<br>Hinxton<br>Cambridge | | |
| Post Code | CB10 1SA | | |
| Telephone | | | |
| Fax | | | |
| Mobile | | | |
| Work Email | [redacted] | | |

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | | [redacted] |
| Post | Director, UCLA Center for Autism Research and Treatment (CART) | | |
| Qualifications | M.D. PhD. | | |
| Employer | Semel Institute for Neuroscience & Human Behavior | | |
| Work Address | 760 Westwood Plaza | | |
| | Semel 68.235 | | |
| | Los Angeles | | |
| Post Code | CA 90095 | | |
| Telephone | | | |
| Fax | | | |
| Mobile | | | |
| Work Email | [redacted] | | |

## A64. Details of research sponsor(s)

### A64-1. Sponsor

**Lead Sponsor**

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

*If Other, please specify:*

**Contact person**

| | |
|---|---|
| Name of organisation | Cambridgshire and Peterborough Foundation Trust and the University of Cambridge |
| Given name | [redacted] |
| Family name | [redacted] |
| Address | Addenbrookes Hospital |
| Town/city | Cambridge |
| Post code | CB2 0QQ |
| Country | UNITED KINGDOM |
| Telephone | [redacted] |
| Fax | |
| E-mail | [redacted] |

### A65. Has external funding for the research been secured?

*Please tick at least one check box.*

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

**Please give details of funding applications.**

| | |
|---|---|
| Organisation | Wellcome Trust |
| Address | 215 Euston Road<br>London |
| Post Code | NW1 2BE |
| Telephone | [redacted] |
| Fax | |
| Mobile | |
| Email | [redacted] |

Funding Application Status: (•) Secured ( ) In progress

Amount: 3,282,994

Duration
Years: 5
Months:

*If applicable, please specify the programme/ funding stream:*

What is the funding stream/ programme for this research project?

**A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ?** *Please give details of subcontractors if applicable.*

( ) Yes (•) No

**A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?**

( ) Yes (•) No

*Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.*

**A68-1. Give details of the lead NHS R&D contact for this research:**

| | Title | Forename/Initials | Surname |
|---|---|---|---|
| | [redacted] | [redacted] | [redacted] |

| | |
|---|---|
| Organisation | Cambridge & Peterborough Foundation Trust |
| Address | Addenbrooks Hospital |
| | Hills Road |
| | Cambridge |
| Post Code | CB2 0QQ |
| Work Email | [redacted] |
| Telephone | [redacted] |
| Fax | |
| Mobile | |

*Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk*

**A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:**

Eastern

*For more information, please refer to the question specific guidance.*

**A69-1. How long do you expect the study to last in the UK?**

Planned start date: 01/04/2020
Planned end date: 01/04/2030
Total duration:
Years: 10 Months: 0 Days: 1

**A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)**

The Spectrum 10K study will be a re-contactable resource. The end of recruitment will be defined as the timepoint following recruitment and enrollment of the 40,000th participant.

**A71-1. Is this study?**

- ○ Single centre
- ◉ Multicentre

**A71-2. Where will the research take place?** *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales

☑ Northern Ireland

☐ Other countries in European Economic Area

Total UK sites in study 20

**Does this trial involve countries outside the EU?**

○ Yes ◉ No

**A72. Which organisations in the UK will host the research?** *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

| | |
|---|---|
| ☑ NHS organisations in England | 18 |
| ☑ NHS organisations in Wales | |
| ☑ NHS organisations in Scotland | |
| ☐ HSC organisations in Northern Ireland | |
| ☐ GP practices in England | |
| ☐ GP practices in Wales | |
| ☐ GP practices in Scotland | |
| ☐ GP practices in Northern Ireland | |
| ☑ Joint health and social care agencies (eg community mental health teams) | 2 |
| ☐ Local authorities | |
| ☐ Phase 1 trial units | |
| ☐ Prison establishments | |
| ☐ Probation areas | |
| ☐ Independent (private or voluntary sector) organisations | |
| ☐ Educational establishments | |
| ☐ Independent research units | |
| ☐ Other (give details) | |
| Total UK sites in study: | 20 |

**A73-1. Will potential participants be identified through any organisations other than the research sites listed above?**

◉ Yes ○ No

**A73-2. If yes, will any of these organisations be NHS organisations?**

◉ Yes ○ No

*If yes, details should be given in Part C.*

**A73-3. Approximately how much time will these organisations expect to spend on screening records and/or provision of information to potential participants, and how will the costs of these activities be funded?**

GP practices will be invited to act as Participant Identification Centres (PIC) sites.
Provision of information to participants will be in the form of an ethically approved study invite letter, information leaflets and posters. GP practices are expected to spend the following time screening and identifying potential participants:

Identifying appropriate practice patients: 15 minutes.

Screening generated participant shortlist: 20 minutes

Mail merge of invite letter to practice patients: 20 minutes.

Study support costs are covered for the study as part of portfolio adoption, and postage will be covered by the Spectrum 10K study.

**A76. Insurance/ indemnity to meet potential legal liabilities**

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

**A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research?** *Please tick box(es) as applicable.*

*Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.*

☑ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

Spectrum 10K is jointly sponsored by Cambridgeshire & Peterborough Foundation Trust & The University of Cambridge. The University of Cambridge will also provide no fault indemnity insurance.

*Please enclose a copy of relevant documents.*

**A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research?** *Please tick box(es) as applicable.*

*Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.*

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

The University of Cambridge will provide no fault indemnity insurance.

*Please enclose a copy of relevant documents.*

**A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?**

*Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.*

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Participants may be recruited through NHS secondary care or tertiary care sites and via primary care. These participants will be covered by NHS indemnity. Alternatively, participants may sign-up online in their home following a PR campaign. For these participants, the University of Cambridge will provide no fault indemnity insurance.

*Please enclose a copy of relevant documents.*

**A78. Could the research lead to the development of a new product/process or the generation of intellectual property?**

○ Yes ○ No ◉ Not sure

## Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

**1. What types of human tissue or other biological material will be included in the study?**

DNA extracted from saliva samples.

**2. Who will collect the samples?**

Study participants and/or consultees/NHS care providers

**3. Who will the samples be removed from?**

☑ Living donors

☐ The deceased

**4. Will informed consent be obtained from living donors for use of the samples?** *Please tick as appropriate*

In this research?

◉ Yes ○ No

In future research?

◉ Yes ○ No ○ Not applicable

**6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?**

○ Yes ◉ No

**8. Will the samples be stored:** *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*

○ Yes ◉ No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*

◉ Yes ○ No

*If Yes, say who will have access to the code and personal information about the donor.*

Predetermined members of the Spectrum 10K research team will have access to the identifiable information of study participants. These will be stored securely and completely separately from samples donated by participants.

In a form in which the donor could be identifiable to researchers?

○ Yes ◉ No

**9. What types of test or analysis will be carried out on the samples?**

We will extract DNA from the saliva samples. This DNA will be used for a range of analyses, including genotype-based, sequencing-based, and methylation-based.

**10. Will the research involve the analysis or use of human DNA in the samples?**

◉ Yes ○ No

**11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?**

◉ Yes ○ No

**12. If so, will arrangements be made to notify the individuals concerned?**

○ Yes ◉ No ○ Not applicable

*If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.*

The Spectrum 10K study does not have the facilities to provide feedback of genetic data in an ethical manner that minimizes distress with the right support and counselling service. All participants are advised within the participant information sheet that they will not receive feedback of genetic results.

**13. Give details of where the samples will be stored, who will have access and the custodial arrangements.**

The samples will be sent to an extraction, storage and genotyping centre such as the NIHR UK BioCentre in Milton Keynes. However, due to uncertainty over availability of storage services due to COVID-19, we may also store samples at the University of Cambridge in -80 C or -20 C freezers. This is to ensure that the study progresses even if centres such as the NIHR UK Biocentre are busy with COVID-19 related testing.

**14. What will happen to the samples at the end of the research?** *Please tick all that apply and give further details.*

☑ Transfer to research tissue bank

*(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)*

☐ Storage by research team pending ethical approval for use in another project

*(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)*

☐ Storage by research team as part of a new research tissue bank

*(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)*

☑ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

*Please give further details of the proposed arrangements:*

All DNA that has been extracted will be stored at a service lab (e.g. UK Biocentre). As only DNA is being stored, an HTA is not needed in line with the HTA act.

https://www.hta.gov.uk/sites/default/files/Code%20E.pdf

## B. All research other than CTIMPs

*In this sub-section, an adult means a person aged 16 or over.*

**B1. What impairing condition(s) will the participants have?**

*The study must be connected to this condition or its treatment.*

Autistic adults with co-occurring intellectual disability (i.e. with reduced capacity). Non-autistic adults with co-occurring intellectual disability who are relatives of participating autistic individuals.

**B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.**

Autistic individuals with intellectual disability (i.e. with reduced capacity) will be included in this study. Non-autistic adults with co-occurring intellectual disability who are relatives of participating autistic individuals will also be included in this study. This represents a group of individuals who are not well represented in scientific studies, and who may differ in their needs from autistic individuals without co-occurring intellectual disability. Biological and environmental contributions to autism, co-occurring conditions, and wellbeing may differ between autistic individuals with and without intellectual disability. To this end, this is an understudied group who need to be included to ensure they are provided with support and care.

**B3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?**

At NHS sites, a member of the direct care clinical team will assess if the person is able to consent for themselves. In the online setting where a person is unable to give consent, a consultee will be requested (family member, carer etc) who is able to act in this capacity for the person with reduced capacity. Capacity will be assessed using the British Medical Association "Assessing mental capacity tool". This will be used in both the face-to-face and online setting. This will be documented within the consent process on the study website.

**B4. Does the research have the potential to benefit participants who are unable to consent for themselves?**

◉ Yes ○ No

*If Yes, please indicate the nature of this benefit. You may refer back to your answer to Question A24.*

There are no direct benefits to participating in this study; however, the information we gain from this study will help to further our understanding of autism. This research may lead to better treatment and diagnostic guidelines and improve future care for autistic individuals.

**B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?**

◉ Yes ○ No

*If Yes, please explain how the research will achieve this:*

The Spectrum 10K study will contribute to knowledge and aim to better understand biological and environment contributions to autism, co-occurring condition, and well being in autism. This will help to identify how genetics interact with the environment to identify trajectories of outcome on autism severity. This in turn will enhance care and treatment pathways for autistic individuals and identify where current need is not being met including for autistic individuals with co-occurring intellectual disability.

**B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?**

○ Yes ◉ No

*Questions B7 and B8 apply to any participants recruited in England and Wales.*

**B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?**

For adults with reduced capacity, a consultee will be required. At NHS sites consultees will either be family members/carers. Using the British Medical Association "Assessing Mental Capacity tool" the need for a consultee will be confirmed by the direct clinical care team. Participants with reduced capacity will be provided with an adapted participant information sheet and the consultee will be provided with a consultee information sheet and consultee declaration form.

In the online setting, the British Medical Association "Assessing Mental Capacity tool" will be used to assess if a consultee is required. It is requested as part of the sign up and consent process. The consultee will be asked to indicate their relationship to the participant and will select from a drop-down menu on the website.

*Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.*

**B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?**

○ Yes ◉ No

*If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or advice from a consultee as soon as practicable thereafter.*

*Question B7-1 applies to any participants recruited in Scotland.*

**B7-1. What arrangements will be made to identify and seek consent from a guardian or welfare attorney or, if there is no such person, from the participant's nearest relative?**

For adults with reduced capacity, a consultee will be requested. At NHS sites this will be performed by either a family member/carer.
Using the British Medical Association "Assessing Mental Capacity tool" the need for a consultee will be confirmed by the direct clinical care team. Participants with reduced capacity will be provided with an adapted participant information sheet and the consultee will be provided with a consultee information sheet and consultee declaration form.

In the online setting, the British Medical Association "Assessing Mental Capacity tool" will be used to assess if a consultee is required. It is requested as part of the sign up and consent process. The consultee will be asked to indicate their relationship to the participant and will select from a drop-down menu on the website.

If a guardian/welfare attorney or relative cannot be identified, then the person will not be eligible to participate in Spectrum 10K.

*Please enclose a copy of the written information to be provided and the consent form to be used. The information sheet should provide information about the research similar to that which might be given to participants able to consent for themselves.*

**B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?**

Members of the direct care team at secondary care sites will review "best interest" participation for participants with reduced capacity.

**B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?**

Easy-read or adapted participant information sheets will be provided to participants with reduced capacity. In addition, consultee participant information sheets and consent forms will also be provided. If it is identified that a consultee is required, they will be asked to consider the wishes and feelings of the participant and act in line with these.

**B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?**

It is unlikely that capacity will fluctuate during the course of the study for participants with co-occurring intellectual disability. Due to the online nature of the study and the lack of follow-up study visits at sites, it is not possible for the capacity of participants to be monitored during the course of the study.

In the unlikely event that a person has loses capacity during the course of the study and the study team is informed, that person will be withdrawn from the study and any data collected up until the point of withdrawal kept, but no further data will be collected.

In the unlikely scenario that a person regains capacity (very unlikely as lack of capacity is primarily due to intellectual disability) during the course of the study they will be provided with an up to date participant information sheet and consent will be sought. If the participant does not wish to participate in the study, they will be withdrawn.

**B12-1. What will be the criteria for withdrawal of participants?**

If a participant requests to withdraw at any time, they will be withdrawn from the study. They do not have to give a reason.

If a consultee informs the study team, that they believe that it is now the preferred wishes of a participant with reduced capacity to no longer participate in the study, that person will be withdrawn.

If an NHS site direct care clinical team indicate that it is their opinion that it is not in the best interests of a person with reduced capacity to remain enrolled in the Spectrum 10K study, they will be withdrawn.

If a participant has withdrawn from the study, they will be asked to stipulate how they would like their data to be stored. Three options will be provided:

No Further Contact:
This means that Spectrum 10K would no longer contact the participant directly but would have permission to retain and use information and samples provided previously and to obtain and use further information from health records.

No Further Access:
This means that Spectrum10K would no longer contact a participant or obtain further information from health records in the future, but still has permission to use the information and samples provided previously.

No Further Use:
In addition to no longer contacting a participant or obtaining further information, any information and samples collected previously would no longer be available to researchers. Spectrum 10K would destroy samples (although it may not be possible to trace all distributed sample remnants) and would only hold information for archival audit purposes. Such a withdrawal would prevent information about the participant from contributing to further research, but it would not be possible to remove data from research that had already taken place.

**B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).**

No study procedures will be performed without a participants explicit consent.

**B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant?** *This question applies to England, Wales and Scotland only – please see guidance notes for further information.*

No study procedures will be performed without a participants explicit consent. A member of the Spectrum 10K study team will be available to discuss all study procedures and to answer any questions participants may have prior to consent.

## PART B: Section 7 - Children

**1. Please specify the potential age range of children under 16 who will be included and give reasons for carrying out the research in this age group.**

2 - 15
Research is being carried out in this age-group to allow insight into autistic individuals across the lifespan. The aim is to understand how autism develops and how genes interact with the environment to produce different outcomes for different people.

**2. Indicate whether any children under 16 will be recruited as controls and give further details.**

Non-autistic children will be recruited if they are family members of a participating autistic individual.

**3-2. Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.**

All participants < 16 years, informed consent will be sought from a parent or legal guardian. Parents will be provided with dedicated participant information sheets and consent forms. For children who turn 16 during the study, parents or legal guardians will be contacted to invite their adult child to consent to remain in the the Spectrum 10K study (if appropriate). This will be monitored through reports within the Spectrum 10K database.

**4. If you intend to provide children under 16 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding.**

Parents will consent for any children under the age of 16 years.

*Copies of written information sheet(s) for parents and children, consent/assent form(s) and any other explanatory material should be enclosed with the application.*

## PART C: Overview of research sites

**Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites.** *For further information please refer to guidance.*

| Investigator identifier | Research site | Investigator Name |
|---|---|---|
| IN1 | ○ NHS/HSC Site<br>◉ Non-NHS/HSC Site | Forename [redacted]<br>Middle name<br>Family name [redacted]<br>Email |
| | Institution name: Medway Community Healthcare<br>Department name:<br>Street address: Bailey Drive<br>Town/city: Gillingham, Kent<br>Post Code: ME8 0PZ<br>Country: UNITED KINGDOM | Qualification (MD...): Registered Nurse RGN<br>Country: UNITED KINGDOM |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England)<br>○ NHS (outside England)<br>○ Non-NHS | NIHR CRN: North East and North Cumbria | E-mail: |

| Investigator identifier | Research site | Investigator Name |
|---|---|---|
| IN2 | ◉ NHS/HSC Site<br>○ Non-NHS/HSC Site | Forename [redacted]<br>Middle name [redacted]<br>Family name<br>Email [redacted] |
| | Organisation name: COVENTRY AND WARWICKSHIRE PARTNERSHIP NHS TRUST<br>Address: WAYSIDE HOUSE<br>WILSONS LANE<br>COVENTRY WEST MIDLANDS<br>Post Code: CV6 6NY<br>Country: ENGLAND | Qualification (MD...): Consultant in Paediatric Neurodisability<br>Country: UNITED KINGDOM |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England)<br>○ NHS (outside England) | NIHR CRN: North West Coast | E-mail: |

◯ Non-NHS

IN3

◉ NHS/HSC Site
◯ Non-NHS/HSC Site

| | |
|---|---|
| Forename | [redacted] |
| Middle name | |
| Family name | |
| Email | [redacted] |
| Qualification (MD...) | Consultant Speech and Language Therapist |
| Country | UNITED KINGDOM |

| | |
|---|---|
| Organisation name | TEES, ESK AND WEAR VALLEYS NHS FOUNDATION TRUST |
| Address | TRUST HEADQUARTERS<br>WEST PARK HOSPITAL<br>EDWARD PEASE WAY<br>DARLINGTON COUNTY DURHAM |
| Post Code | DL2 2TS |
| Country | ENGLAND |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England) | NIHR CRN: Yorkshire and Humber | |
| ◯ NHS (outside England) | | E-mail: |
| ◯ Non-NHS | | |

IN4

◉ NHS/HSC Site
◯ Non-NHS/HSC Site

| | |
|---|---|
| Forename | [redacted] |
| Middle name | [redacted] |
| Family name | |
| Email | [redacted] |
| Qualification (MD...) | Consultant MD |
| Country | UNITED KINGDOM |

| | |
|---|---|
| Organisation name | CAMBRIDGESHIRE AND PETERBOROUGH NHS FOUNDATION TRUST |
| Address | ELIZABETH HOUSE, FULBOURN HOSPITAL<br>CAMBRIDGE ROAD<br>FULBOURN CAMBRIDGE CAMBRIDGESHIRE |
| Post Code | CB21 5EF |
| Country | ENGLAND |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England) | NIHR CRN: Eastern | |
| ◯ NHS (outside England) | | E-mail: |

○ Non-NHS

IN5

● NHS/HSC Site
○ Non-NHS/HSC Site

Forename [redacted]
Middle name [redacted]
Family name
Email [redacted]

| | |
|---|---|
| Organisation name | CHESHIRE AND WIRRAL PARTNERSHIP NHS FOUNDATION TRUST |
| Address | TRUST BOARD OFFICES<br>UPTON LEA RESOURCE CENTRE<br>THE COUNTESS OF CHESTER HEALTH PARK<br>CHESTER CHESHIRE |
| Post Code | CH2 1BQ |
| Country | ENGLAND |

Qualification (MD...): Consultant Psychiatrist.
Country: UNITED KINGDOM

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ● NHS (England)<br>○ NHS (outside England)<br>○ Non-NHS | NIHR CRN: East Midlands | E-mail: |

IN6

● NHS/HSC Site
○ Non-NHS/HSC Site

Forename [redacted]
Middle name
Family name [redacted]
Email [redacted]

| | |
|---|---|
| Organisation name | THE ROYAL WOLVERHAMPTON NHS TRUST |
| Address | NEW CROSS HOSPITAL<br>WOLVERHAMPTON ROAD<br>HEATH TOWN<br>WOLVERHAMPTON WEST MIDLANDS |
| Post Code | WV10 0QP |
| Country | ENGLAND |

Qualification (MD...): MD
Country: UNITED KINGDOM

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ● NHS (England) | NIHR CRN: West of England | |

| | | |
|---|---|---|
| ◯ NHS (outside England) | | E-mail: |
| ◯ Non-NHS | | |

IN7

◉ NHS/HSC Site
◯ Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | [redacted] |
| Organisation name | MEDWAY | Qualification (MD...) | MD |
| Address | MEDWAY MARITIME HOSPITAL<br>WINDMILL ROAD<br>GILLINGHAM KENT | Country | UNITED KINGDOM |
| Post Code | ME7 5NY | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England) | NIHR CRN: Kent, Surrey and Sussex | |
| ◯ NHS (outside England) | | E-mail: |
| ◯ Non-NHS | | |

IN8

◯ NHS/HSC Site
◯ Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | |
| | | Qualification (MD...) | MD |
| | | Country | UNITED KINGDOM |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England) | NIHR CRN: Thames Valley and South Midlands | |
| ◯ NHS (outside England) | | E-mail: |
| ◯ Non-NHS | | |

IN9

◯ NHS/HSC Site
◯ Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | [redacted] |
| | | Qualification (MD...) | Consultant in Paediatric Neurodisability |
| | | Country | UNITED KINGDOM |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England) | NIHR CRN: Wessex | |
| ○ NHS (outside England) | | E-mail: |
| ○ Non-NHS | | |

IN10

○ NHS/HSC Site
○ Non-NHS/HSC Site

Forename [redacted]
Middle name
Family name [redacted]
Email [redacted]
Qualification (MD...) Clinical Specialist Occupational Therapist
Country UNITED KINGDOM

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England) | NIHR CRN: South West Peninsula | |
| ○ NHS (outside England) | | E-mail: |
| ○ Non-NHS | | |

IN11

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename [redacted]
Middle name
Family name [redacted]
Email [redacted]
Qualification (MD...) Consultant Paediatrician
Country UNITED KINGDOM

Organisation name: UNIVERSITY HOSPITALS PLYMOUTH NHS TRUST
Address: DERRIFORD HOSPITAL, DERRIFORD ROAD, PLYMOUTH DEVON
Post Code: PL6 8DH
Country: ENGLAND

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| ◉ NHS (England) | | |
| ○ NHS (outside England) | | E-mail: |
| ○ Non-NHS | | |

IN12

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename [redacted]
Middle name [redacted]

| | | | |
|---|---|---|---|
| | | Family name | [redacted] |
| | | Email | |
| Organisation name | EAST SUSSEX HEALTHCARE NHS TRUST | Qualification (MD...) | MD |
| Address | ST. ANNES HOUSE<br>729 THE RIDGE<br>ST. LEONARDS-ON-SEA<br>EAST SUSSEX | Country | UNITED KINGDOM |
| Post Code | TN37 7PT | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (•) NHS (England)<br>( ) NHS (outside England)<br>( ) Non-NHS | | E-mail: |

IN13

(•) NHS/HSC Site
( ) Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | |
| | | Middle name | |
| | | Family name | |
| | | Email | |
| Organisation name | DERBYSHIRE HEALTHCARE NHS FOUNDATION TRUST | Qualification (MD...) | |
| Address | TRUST HEADQUARTERS<br>KINGSWAY HOSPITAL<br>KINGSWAY DERBY<br>DERBYSHIRE | Country | |
| Post Code | DE22 3LZ | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (•) NHS (England)<br>( ) NHS (outside England)<br>( ) Non-NHS | | E-mail: |

IN14

(•) NHS/HSC Site
( ) Non-NHS/HSC Site

| | |
|---|---|
| Forename | [redacted] |
| Middle name | |
| Family name | [redacted] |
| Email | [redacted] |

| | | | |
|---|---|---|---|
| Organisation name | SURREY AND BORDERS PARTNERSHIP NHS FOUNDATION TRUST | Qualification (MD...) | Consultant Psychiatrist, Clinical Lead |
| Address | 18 MOLE BUSINESS PARK<br>RANDALLS ROAD<br>LEATHERHEAD SURREY | Country | UNITED KINGDOM |
| Post Code | KT22 7AD | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (•) NHS (England)<br>( ) NHS (outside England)<br>( ) Non-NHS | | E-mail: |

IN15

(•) NHS/HSC Site
( ) Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | [redacted] |
| Organisation name | SOMERSET PARTNERSHIP NHS FOUNDATION TRUST | Qualification (MD...) | MD |
| Address | 2ND FLOOR<br>MALLARD COURT<br>EXPRESS PARK, BRISTOL ROAD BRIDGWATER SOMERSET | Country | UNITED KINGDOM |
| Post Code | TA6 4RN | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (•) NHS (England)<br>( ) NHS (outside England)<br>( ) Non-NHS | | E-mail: |

IN16

(•) NHS/HSC Site
( ) Non-NHS/HSC Site

| | |
|---|---|
| Forename | [redacted] |
| Middle name | |
| Family name | [redacted] |
| Email | [redacted] |

| | | | |
|---|---|---|---|
| Organisation name | HERTFORDSHIRE PARTNERSHIP UNIVERSITY NHS FOUNDATION TRUST | Qualification (MD...) | Professor of Psychology |
| Address | 99 WAVERLEY ROAD<br>ST. ALBANS<br>HERTFORDSHIRE | Country | UNITED KINGDOM |
| Post Code | AL3 5TL | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (●) NHS (England)<br>( ) NHS (outside England)<br>( ) Non-NHS | | E-mail: |

IN17

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | [redacted] |
| Organisation name | BARTS HEALTH NHS TRUST | Qualification (MD...) | Consultant Paediatrician. |
| Address | THE ROYAL LONDON HOSPITAL<br>WHITECHAPEL<br>LONDON GREATER LONDON | Country | UNITED KINGDOM |
| Post Code | E1 1BB | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (●) NHS (England)<br>( ) NHS (outside England)<br>( ) Non-NHS | | E-mail: |

IN18

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | [redacted] |
| Organisation name | POOLE HOSPITAL NHS FOUNDATION TRUST | Qualification (MD...) | MD |

| | | | |
|---|---|---|---|
| Address | LONGFLEET ROAD | Country | UNITED KINGDOM |
| | POOLE DORSET | | |
| Post Code | BH15 2JB | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (•) NHS (England) | | |
| ( ) NHS (outside England) | | E-mail: |
| ( ) Non-NHS | | |

IN19

(•) NHS/HSC Site
( ) Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | [redacted] |
| Organisation name | CORNWALL PARTNERSHIP NHS FOUNDATION TRUST | Qualification (MD...) | Speech & Language Therapist. |
| Address | PORTHPEAN ROAD | Country | UNITED KINGDOM |
| | ST AUSTELL CORNWALL | | |
| Post Code | PL26 6AD | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (•) NHS (England) | | |
| ( ) NHS (outside England) | | E-mail: |
| ( ) Non-NHS | | |

IN20

(•) NHS/HSC Site
( ) Non-NHS/HSC Site

| | | | |
|---|---|---|---|
| | | Forename | [redacted] |
| | | Middle name | |
| | | Family name | [redacted] |
| | | Email | [redacted] |
| Organisation name | KENT COMMUNITY HEALTH NHS FOUNDATION TRUST | Qualification (MD...) | Consultant Community Paediatrician and Clinical Director |
| Address | UNIT D, THE OAST | | |
| | HERMITAGE COURT | Country | UNITED KINGDOM |
| | BARMING MAIDSTONE KENT | | |
| Post Code | ME16 9NT | | |
| Country | ENGLAND | | |

**Participant Identification Centres**

| PIC Type | Centre | Individual(s) |
|---|---|---|
| (●) NHS (England) | | |
| ( ) NHS (outside England) | | E-mail: |
| ( ) Non-NHS | | |

## PART D: Declarations

**D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

**Contact point for publication***(Not applicable for R&D Forms)*

*HRA would like to include a contact point with the published summary of the study for those wishing to seek further*

*information. We would be grateful if you would indicate one of the contact points below.*

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

**Access to application for training purposes** *(Not applicable for R&D Forms)*

*Optional – please tick as appropriate:*

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by [redacted] on 02/06/2020 17:56.

| | |
|---|---|
| Job Title/Post: | Professor of Developmental Psychopathology, Director |
| Organisation: | Autism Research Centre |
| Email: | [redacted] |

**D2. Declaration by the sponsor's representative**

*If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.*

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by [redacted] on 03/06/2020 09:51.

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|---|---|
| Job Title/Post: | Research Governance Coordinator |
| Organisation: | CPFT |
| Email: | [redacted] |