IMAGINE ID
Intellectual Disability and Mental Health: Assessing Genomic Impact on Neurodevelopment

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Sponsor:
University of Cambridge and Cambridge University Hospitals NHS Trust

Funder:
Medical Research Council

Protocol 5.0 13.12.2016

Background and need for research in this area:

Nature and importance of challenge – Summary:

Intellectual disability (ID) is defined as "significant limitations both in intellectual functioning and in adaptive behaviour, which covers many everyday social and practical skills" and originates before the age of 18 years. In 2010, there were estimated to be 1,198,000 people with intellectual disabilities (ID) in England, of whom 298,000 were children under 18 years of age. The proportion of ID that can be entirely or in large part accounted for by genetic factors may reach 85%, of which a proportion is due to minor chromosomal structural anomalies known as copy number variations-CNVs which contribute 10-15 % and the remainder are due to single nucleotide variants (SNVs), many of which constitute novel genomic disorders. Interrogation of the genome at high resolution to detect submicroscopic chromosomal imbalances is now a first-line recommended diagnostic test in ID; array comparative genomic hybridization (aCGH) indicates that ~14% of ID investigated during childhood is caused by CNVs >400 kb. Despite strong evidence for pathogenicity, we know little about the spectrum of lifespan difficulties in CNV-associated ID or in pathogenic variants in single genes. Existing databases (e.g. DECIPHER) record newly discovered anomalies to assist in judging pathogenicity of novel variants, but they lack phenotypically rich information to assist in prognostication and health service planning. We urgently need to delineate the course and outcomes in CNV-associated ID and single gene disorders to provide information at the point of diagnosis and onwards for families, clinicians and service providers, as well as to pave the way to greater biological understanding and the personalization of interventions. We will address and rectify these deficiencies in a novel design that minimizes cost and provides remarkable value for money.

The need for research into mental health risks of CNVs and/or SNVs in ID, how this will further our understanding and lead to better care in the future:

Previous research has shown that lifestyle transitions (e.g. early admission to residential services, transfer to out-of-area placements) and quality of life (e.g. occupation, relationships, community integration) for individuals with ID and their carers are strongly influenced by: i) poor adaptive function ii) challenging behaviour, and iii) co-morbidity, particularly of psychiatric illness. These three key outcomes are highly variable within the ID population and contribute substantially to the £6.5 billion p.a. cost of care and support for people with ID and their families. Several recurrent ID-associated CNVs and single gene disorders have been associated with poor mental health outcomes, but there is considerable pleiotropy and incomplete penetrance for specific psychiatric diagnoses including autism, psychosis, attention deficit hyperactivity disorder, and for non-psychiatric including intellectual impairment itself, sensory impairments and epilepsy. No study to date has deployed systematic sampling and assessment to determine why some, but not all, ID-related CNVs and single gene disorders are associated with poor mental health outcomes, nor have they identified risk and resilience factors modifying outcomes across this population. Assessing the relative contributions of CNV and/or SNV genotype, ID severity, cognitive profile, social/environmental risk factors, and physical comorbidities, will highlight major determinants of adjustment. Better care could be provided if those individuals at greatest risk were identified early and if preventive intervention was timely and focused on salient biological and/or social processes. Early identification has the potential to reduce the costs of long-term care, better target key services/interventions, and improve quality of life over the life-course.

The approach to be taken and how it makes the best use of existing resources:

Our study will leverage a major opportunity presented for the study of the impact of CNVs and SNVs by utilizing data on the large numbers of individuals with ID, especially children, tested by NHS UK genetics services. We will combine these resources with internet-based population phenotyping over time. Our approach will take advantage of existing resources in terms of genotyped individuals and in terms of already-developed, validated, reliable, inexpensive and appropriate methodologies for phenotyping that can be applied to both large-scale and small-scale samples of ID individuals in childhood and adulthood. They offer remarkable value for

money, given the proposed scale of the operation, because they build on existing NHS resources, genotyping availability, and take advantage of recent developments in online testing, in a country where 80% of families have internet access at home.

Background to this specific research study:
The IMAGINE ID (Intellectual Disability and Mental Health: Assessing the Genomic Impact in Neurodevelopment) study is a large scale cohort study which aims to identify the genetic contribution to long-term mental health outcomes in children with intellectual disability who have been investigated within the NHS.
The original grant application to the MRC (June 2013) for this specific call aimed to recruit 10,000 families to this study.
We were awarded pilot funding (March 2014) to test all the measures we plan to use and test out the logistical needs required to achieve this level of recruitment.
We have since received full funding for the project from 1 December 2015 to recruit 5-10,000 cases, having successfully completed the pilot phase of 500 recruits.

In the pilot phase we aimed to test all aspects of the study such that recruitment of the full 5-10,000 families dovetailed seamlessly from the pilot phase.

The pilot study objectives were:
1. To obtain ethical and R&D approvals for the research procedures, based on a limited set of regional populations in the first instance.
2. To demonstrate the feasibility of recruiting families with children meeting eligibility criteria, via two Regional Genetics Centres (RGCs) that represent a comprehensive range of urban and rural environments.
3. To establish recruitment rates, participation rates and completion rates, to identify factors associated with dropout, and to determine the level of support required from the study team to maximize completion rates in families from a range of socioeconomic and educational backgrounds.
4. To develop a secure NHS governance-compatible database of cases with intellectual disability and abnormal CNV or rare genetic variants who have been consented for research. To develop an online data collection facility that is secure, user-friendly, reliable and flexible.
5. To obtain online pilot data, measuring critical phenotypic outcome and predictor variables, in order to evaluate the feasibility of testing the hypotheses outlined in the original application in a large population at minimal cost.
6. To validate the online outcome and predictor measures by means of offline face-to-face assessments.
7. To obtain R&D permissions and confirmed collaborative agreements to recruit eligible children with CNV and SNVs from all 24 RGCs throughout the UK and through Unique, the international support charity and DECIPHER, an online database of genetic anomalies by the end of this pilot project.

The main phase study objectives are:
1. To maintain successful recruitment rates, participation rates and completion rates and continue to support families from a range of socioeconomic and educational backgrounds to maximize completion rates to reach the aim of 5-10,000 recruits.

Study participants:
The criteria for inclusion in the study are:

1. Has generalised intellectual disability diagnosis with a specialist physician (+/- comorbidities, such as autism etc.)
2. Has had a diagnostic microarray analysis of DNA by an accredited laboratory
3. Is at least 3 years of age at ascertainment. If participant is resident in Scotland and lacks capacity the recruitment age limit is 16 years.

4. Has at least one CNV and/or SNV reported as being clinically significant or has a pathogenic sequence variant
5. Can be traced and is willing to participate
6. The results of the abnormal array or sequence abnormality has been communicated to the family by a healthcare professional before the date of recruitment.

Exclusion criteria are:

1. Those individuals not matching the above inclusion criteria.

Study Procedures

Recruitment through Regional Genetics Centres:

1. Data from the UK-wide Regional Genetics Centres (RGCs) will be the source for targeted recruitment.
2. A list of unlinked data will be generated on a monthly basis from each RGC containing a list of all the genomic coordinates of patients with intellectual disability who have had a diagnostic result which has been reported to be clinically significant and associated with intellectual disability.
3. A list of unlinked data of the postcodes of all cases where an abnormal result has been issued in the same period. This data will be used to understand the demographics of the population we are recruiting and to understand the social / educational profiles of those who take part and those who do not. This data will not be used to identify individuals.
4. For retrospective recruitment, a standard letter of invitation to the study will be generated by the clinician for all cases that meet criteria for recruitment. The letter of introduction will be sent by the clinician to inform potential participants about the study.
5. For prospective recruitment, healthcare professionals (i.e. research nurses, doctors, genetic counsellors) can give families the standard invitation booklet during clinic appointments along with the PIS and consent form to consider, ask questions, complete and send back if they wish to participate in the study. Alternatively, the clinicians and potential participant can complete a form that the potential participant signs to give permission for their contact details to be forwarded to the research coordinators.

Recruitment through DECIPHER and Unique support group

1. DECIPHER http://decipher.sanger.ac.uk/ is a Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources which has been developed over the past 10 years and is maintained to collate cases with microdeletions and duplications and genomic coordinates associated with developmental delay. >80% have some degree of intellectual impairment and this database is regularly updated with data from UK cases diagnosed through the RGCs where families have consented for data to be logged and seen. Through the established collaboration with DECIPHER we will specifically recruit UK families who have registered their interest in taking part in research. DECIPHER holds genotype and phenotype data, and the origin of the sample with respect to the RGC but not the specific patient contact details. Recruitment will be through UK RGCs where the genotype is the source of recruitment.
2. Unique is the rare chromosomal abnormality support group http://www.rarechromo.org/. Unique are key collaborators in the grant and have offered advice throughout the design and grant application stage and are supportive of the research project. Unique have hosted a trial group of parents who will assist in web design and online portal assessments during the project to identify the best design and functionality, and will support advertising of the study to its members. Recruitment to the study will be direct to the web address or through the RGCs.

Methods of consenting and online assessments for all participants once identified through the range of methods:

1. Participants will be offered multiple ways of being recruited depending on their preferred mode of communication.
2. Depending on the preferred mode of communication indicated by interested participants, a copy of the PIS, age-appropriate consent forms and participant details form can be sent via email or in the post. The research team will be available to discuss all aspects of the study via email, face-to-face or by telephone interview. Once informed consent has taken place, forms will be completed and sent to the appropriate study centre (i.e. either the Cambridge research team or the potential participant's RGC) to begin recruitment. Potential participants and families will supply email or telephone contact details so that the research team can contact patients recruited through the above listed range of methods to ensure informed consent has taken place.
3. Once recruited, families will be given a unique identifier and password to enter the research website where the study data will be entered using a secure web interface. They will then have direct access to the online questionnaires about their child and the nature of the genetic abnormality.
4. We have developed a secure website so that patients can register their interest in taking part in the study online. Personal data on each participant is uploaded to a secure database within seconds of entry so that personal data will not be stored in the public web space. If participants express an interest in taking part in the study, they will send an email to a specific address. This will then generate an email exchange with the study team to register the family's interest in taking part and for the research team to establish the interest is bona fide. If the participant is genuine and it is clear they are interested, they will complete the consent form having received the participant information and had time to consider taking part. Consent and discussion online and by email will be available as will a telephone hot line to ensure participants can have all their questions answered appropriately and thus informed consent is achieved. Once consent has taken place, documentation of the consent will be sent to the referring clinician by post or nhs.net email to be filed as a pdf document in the hospital records. Participants will have the option of how to receive a copy of their consent; either by post, by an email or by preset exchange of text messages which documents their agreement to take part in the study and their signed consent form. This method will not involve the exchange of confidential personal details.
5. Parents of affected children are the key participants and thus for children <16 years consent is for the parents to complete the forms and questionnaires about their children with ID. For children >16 years the level of disability is likely to be moderate to severe and thus parents or carers are most likely to be the only ones able to complete the questionnaires. As children >16 years with capacity would be able to consent for their parents to report on their behalf, we have included forms for children >16 years who have capacity. We do not think it is likely that many children >16 years will be able to complete the questionnaires themselves nor are the questionnaires validated for self-assessment, but wish to respect their right to give or refuse consent for the data collection.

Online phenotyping and data collection:

1. All measures in the online pilot study can be administered offline, if participating families do not have access to the internet. As discussed in the original application, we will obtain demographic data about both the index child and their family, including the health and education of the affected child, comprising the individual educational statement of support, their medical and educational history, psychomotor development, communication skills and contact with support services.
2. Parental reports of their child's behavioural adjustment and mental health will be obtained using the DAWBA (Diagnostic and Well-Being Assessment) that has been used in both UK national and international surveys of mental health in typical and ID

children (Ford,T., et al. J. Am. Acad. Child Adolesc. Psychiatry 42, 1203-1211 (2003);Green,H., et al. Mental Health of Children and Young People in Britain, 2004;Heiervang,E., et al. J. Child Psychol. Psychiatry 49, 678-685(2008);Emerson,E. & Hatton,C. Br. J. Psychiatry 191, 493-499 (2007)).This methodology has been used successfully to gather data of high quality by parental online reporting. Making a clear distinction between problem behaviour in general, and psychiatric disorders in particular, is important in the ID population. We will use a validated automated diagnostic algorithm system devised for this purpose, compatible with ICD-10/DSM-IV and V. The DAWBA will be supplemented by additional measures tailored to record behaviour found mainly in severely and profoundly ID children (e.g. repetitive self-injury). Details of the DAWBA and its range of assessments are available in over 20 languages (http://www.dawba.com/), and we do not intend to exclude families on the basis of ethnicity or inability to speak/understand English.

3. Physical development, medical comorbidity and service usage will be recording using an online questionnaire developed by IMAGINE ID. Data include: birth, physical development and anomalies, metabolic systems, sensory abnormalities, psychomotor development, communication skills, services and intervention, medical history. Free text entry is available. Ethnicity and immigration status will also be recorded (the latter a recently identified risk factor for child mental health).
4. Developmental status/Cognitive functions: Draw-a-Person: Quantitative Scoring System (DAP:QSS)- the draw a person test is a non-verbal test to evaluate intelligence in children. Participating children are asked to complete 3 drawings: a picture of a man, a woman and themselves. The instructions are minimal and easy to understand: “I want you to make a picture of a person. Make the very best picture that you can. Take your time and work very carefully. Try very hard and see what a good picture you can make.” For each picture the child is asked to draw a full person (e.g. head to feet). There is no time limit but children rarely take longer than 10-15 minutes to complete all 3 drawings. The DAP:QSS is both valid and reliable (Goodenough, 1963; Naglieri, 1988; Naglieri and Maxwell, 1981; Jolley, 2010) and correlates with face to face IQ measures including the WISC-R and WISC-III (Abell, Wood, & Liebman, 2001).
5. Adaptive skills: ABAS-III wherein participant’s parents will be asked to complete the Adaptive behavior assessment system (ABAS) III online, released online for the first time this year. The ABAS III measures adaptive skills across the life span in detail. It covers three broad domains (conceptual, social and practical). Within these domains, it assesses 10 skill areas. Items focus on practical, everyday activities required to function, meet environmental demands, care for oneself, and interact with others effectively and independently. On a 4-point response scale, raters indicate whether, and how frequently, the individual performs each activity. Oakland, T., & Harrison, P. L. (Eds.). (2011). Adaptive behavior assessment system-II: Clinical use and interpretation. Academic Press.
6. Social circumstances: Potential modifying factors associated with mental health problems and challenging behaviour in ID include family discord, socioeconomic deprivation, life events and parental stress. All this information is captured by the DAWBA, in a form that is acceptable to families (Esbensen,A.J. & Benson,B.A. J. Intellect. Disabil. Res. 50, 248-258 (2006);Koskentausta,T., et al. J. Intellect. Disabil. Res. 51, 43-53 (2007);Hastings,R.P et al. J. Autism Dev. Disord. 35, 635-644 (2005)).
7. Where parents do not live together we will attempt to contact both biological parents, with the appropriate permissions. We will review and revise these cognitive measures taking into account the social circumstances pertaining to the cohort population, or if excessive support is found to be required to achieve the online data collection.
8. Questionnaire timescales for completion include i) demographics of parents, child (10mins) ii) medical history of the child (30 mins) iii) genomic details of the child’s abnormality and parental information about inheritance (5mins) iv) DAWBA (Development and Wellbeing assessment (60-120 mins) v) ABAS III (30 mins). vi)

Draw a person (10-15 mins).
The questionnaires are standardised, peer reviewed, published and validated and are extensively used. The website will permit save and return to the data entry permitting completion over several visits to the web.

9. On completion of the questionnaires the results will be reviewed by the research team and a summary of the findings will be sent to the participant families and the referring clinician.
10. For families who need assistance in completing the questionnaire, options will be available which include telephone advice as to how to fill out the forms or the option of a telephone interview to complete the forms if this is preferred. Home visits may be offered to complete the forms if needed. Detailed records of the nature of assistance will be recorded for all participants and will form part of the data set to judge the ease of this method of data collection. The team of staff to assist in the recruitment and completion of the forms will include an experienced research study coordinator and psychology graduates who are all experienced in interacting with families with a child with intellectual impairment and can answer questions and manage any distress caused by taking part in the study.

Website design and content:

1. The research team developed content for the website within the first year of the project and this has now been launched as the main portal for recruitment after the pilot phase.
2. The website aims to inform about the project and to provide access for recruitment.
3. Menu headings include: Home, Taking part information, Can my family take part?, What will we be asked to do?, We are interested what should we do next?, How will my child benefit?, FAQs, Healthcare Professionals information, Study documents & Downloads, News/Events, Contact information, About Us and Further research, information & support.
4. The consent forms, participant details and PIS are available to download.

Further study of a subset of participants:

1. Once the online questionnaires are complete, the family have the option to sign up or decline an additional face-to-face interview in the future. We aim to recruit 500 cases who have completed the online questionnaire.
2. Face-to-face interviews will be arranged with families. Researchers will arrange to go to the family home. Interviews of parents and child will take approx. 4 hours and will be performed either as a single visit or multiple visits; depending on the needs of the family. Standardised published tests will be used and will include **CAPA, ADI-R, WASI, WCST and CANTAB.** These interviews will be audiotaped and transcribed as part of the validation study.

Face-to-face study of 500 participants for detailed analysis of phenotypes in ID with a known genetic cause:

This arm of the study will be run by experienced colleagues who are already performing most of the detailed psychometric testing in another study under a separate ethics with Prof M Van Den Bree, University of Cardiff: ECHO 09/WSE04/22. This arm of the study will subsample up to 500 families having completed the online tests. A specialist research team will assess them. The main purpose is to validate and cross reference our online assessment procedures with supplementary offline procedures. A subsidiary aim is to identify whether there are other key phenotypic variables that should be incorporated into the online assessments.
Data collection will include:

Summary of face-to-face assessments

Multiple informant data will be obtained to ensure greater precision and reliability of assessment. All interviews will be taped for further evaluation in team meetings led by child

psychiatrists. All instruments have been selected because they are well-established, published and have performed well in our genetic and other studies of psychopathology and neuropsychology, and are reliable in the age and intellectual ability ranges of the proposed sample.

Parental reports: Questionnaire-assessed child psychopathology, prenatal factors and pubertal development, self-report psychopathology

The primary caretaker (usually mother) will provide information on the child and their environment, including:

1. Family size and structure, social class, pregnancy and child birth (age at birth, birth weight, ante- and perinatal health problems, smoking and alcohol use, as collected by with the modified Lewis scale) [1].
2. Life Events Checklist to screen for possible traumatic events experienced by the child [2].
3. Family relationship quality i.e. overall family relationship quality (Family Environment Scale)[3] and parent child relationship quality (warmth and hostility)(Iowa Family Interaction Rating Scales)[4].
4. Child prosocial and antisocial behaviour, ADHD and emotional symptoms by completing the Strengths and Difficulties Questionnaire (SDQ)[5].
5. Child development and behavioural problems with the Developmental Behaviour Checklist (DBC)[6, 7], which was developed specifically for children with intellectual disability.
6. The Social Communication Questionnaire (SCQ; formerly Autism Screening Questionnaire (ASQ)) [8] will be used to screen for autism.
7. Child pubertal development will be obtained by Peterson assessment [9].
8. Development Coordination Disorder using the Development Coordination Disorder Questionnaire [10].
9. Child eating style and behaviour, with the Child Eating Behaviour Questionnaire (CEBQ)[11] and the Hyperphagia Questionnaire (HQ)(REF).
10. Epilepsy and seizures using the Epilepsy screening questionnaire.
11. Record of medication, operations, contact details of GP, school and 6 screening questions about current state of health.

Parental reports: Interview-assessed child psychopathology

The Child and Adolescent Psychiatric Assessment (CAPA)[12] will be conducted with the primary caretaker. The CAPA (duration 1-2 hours) provides DSM-IV and ICD-10 diagnoses of all behavioural and psychiatric problems (including detailed assessment of psychotic symptoms), except autism. In older children, we will obtain information on prodromal symptoms using the Structured interview for Prodromal Symptoms (SIPS) [13, 14].
Where screening by SCQ is positive, the standardized semi-structured Autism Diagnostic Interview–Revised (ADI-R) will be conducted (duration 1-2 hours)[15].

Parental report: Interview-assessed own and partner psychopathology

The 'Family Structure and function' section of the CAPA [12] will be conducted with the primary caretaker regarding any psychiatric problems faced by themselves and the second caretaker, if applicable. This section provides DSM-IV and ICD-10 diagnoses of the following psychopathology: depression, anxiety, panic disorders, eating disorders, drug or alcohol use and psychosis.

Child reports: Self-report of psychotic symptoms, mood and anxiety and pubertal development in cases and controls

Where possible, we will obtain self-report on psychotic, mood and anxiety disorder and symptoms using the CAPA. Information on pubertal development will be obtained by Peterson assessment [9].
If probands screen positive for autism, in combination with the ADI-R interview conducted with the parents, we will offer the parent the possibility to conduct an observational assessment of the child, to establish autism, using the Autism Diagnostic Observation Schedule (ADOS)[16, 17]. The ADOS is a semi-structured, standardised assessment of communication, social interaction and play. It provides a series of standardised contexts in which the child's social, communication and repetitive, stereotyped behaviours can be observed. Standardised toys and activities are used to present opportunities for social and communicative interaction with the examiner.

Teacher reports

Teachers will be asked to complete a consent form agreeing to complete a questionnaire about their pupils if the participant agrees that the teacher can be approached. We provide a consent form for teachers. Once agreed teachers are asked to complete a brief teacher-version of the Strengths and Difficulties questionnaire (SDQ)[5] and further information on child development specifically suited for cognitively impaired children with the Developmental Behaviour Checklist (DBC)[6, 7].

Neurocognitive assessment and fine motor skills

Children's' IQ will be assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)[18]. The Wisconsin Card Sorting Test (WCST)[19] will be administered to assess executive function and the following Cambridge Neuropsychological Test Automated Battery (CANTAB)[20] tests: Delayed Matching to Sample test (visual memory); Stockings Of Cambridge (spatial planning and working memory); Spatial Working Memory (executive function); Rapid Visual information Processing (attention and general performance); Stop Signal Task (decision making and response control). The full neurocognitive assessment may take up to 2.5 hours. We will therefore conduct the assessment over two days (each day consisting of one half hour session, a break and another half hour session). Depending on the child's mental and motivational state no CANTAB tests or a subset will be offered (individual tests take about seven minutes).
We will also measure fine motor skills, using an assessment that has been used extensively in the Born in Bradford study (http://www.borninbradford.nhs.uk/about-the-project/) and consists of a series of tasks which require the participant to interact with the touch screen of a portable tablet computer using a stylus (i.e. like a pen with paper). The test investigates motoric as well as cognitive aspects of the participant's performance.

Body measurements

We will measure height, weight and head circumference of children and their sibling(s) (if present). Height will be measured using a height measure. Weight will be measured using scales. Head circumference will be measured using a cloth tape. Measurements will be collected using standardized procedures to ensure measurement technique is consistent.

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Data analytic framework:

1. Where ever possible for the data analysis, samples, cases or genomic coordinates will be give unique identifiers which do not identify the name of the patient. All large data handling and analysis will use these unique identifiers. However, linked tables will be available to a limited number of researchers in order to safely manage the recruitment and patient-facing interactions. For example, recruiters will be able to identify whether callers are recruited and at what stage of data entry they have reached. This data will be protected under the Data Protection Act and appropriate research governance.
2. Descriptive statistics: the majority of data captured in the study of families identified from the RGCs will be descriptive, much of it qualitative. We have established, during

the pilot, descriptive information about the accessibility of relevant records and the existence of contact information. The study is recruiting from participating RGCs, and we are able to identify the likely sources of bias in responses from families interested in participation in principle. We will develop protocols to attenuate this bias. Subsequently, we will be able to state with confidence the potential losses due to difficulties obtaining consent for participation in the online testing process. We will ascertain what proportion of families can actually complete the online assessments (and what degree of support is required).

3. Quantitative statistics: criteria validity of online measures will be established. There are several potential sources of invalidity. First, there is the potential unsuitability of the online measure to achieve its intended purpose, such as the use of the DAWBA for assessing psychiatric adjustment in an intellectually disabled population. Second, there is the potential incapacity of parents to report accurately on their child's developmental attainments (e.g. reporting with the PEDS-online test). Third, there is the potential incapacity of individuals to complete accurately an online test of cognitive skills). Standard statistical techniques will be employed in the assessment of validity.

Management plan:

In the pilot study the research groups based in Cambridge, Cardiff and London worked on an integrated way to ensure that the work was conducted efficiently, and delivered the information requested by the MRC within the requisite timescale. Three-monthly face-to-face management meetings were established during the pilot phase and subsequent weekly teleconferences between the Principal Investigators currently take place. The London team continue to oversee the establishment and functional integration of the online assessments and their associated database, and associated training of all staff. As requested by the Board, the primary focus of the pilot project was on the feasibility of recruitment, and on the feasibility of completing online assessments. This entailed obtaining ethical/R&D permission for access to RGC records, and establishing personal links with all 22 collaborating RGCs. This work has been led by the Cambridge team who are also the main contact point for participating families. Cambridge also take the lead in training the team responsible for searching records, interpreting molecular genetics data and providing the initial contacts, recruitment and the ongoing genetic support to eligible families during the project. The Cambridge team will also take responsibility for supporting the London team in the supervision of online assessments during home visits. Cardiff will take the lead in training and monitoring the work of the research team responsible for off-line measures (validity study).

Data collection, storage and long-term maintenance of the cohort:

1. The online collection of data will be over a secure server. Data that is entered by participants will be held briefly within the internet and then delivered to a secure database within seconds of data entry. Initially the online data entry will be from patients who have been recruited through the RGCs. However, it is likely that families may wish to self-refer and thus names and contact details will be entered into the database by participants as a means of recruitment. Data will be stored in a database compliant with the Data Protection Act 1998, The common law duty of confidentiality, The Confidentiality NHS Code of Practice, The NHS Care Record Guarantee for England, The Social Care Record Guarantee for England, The international information security standard: ISO/IEC 27002: 2005, The Information Security NHS Code of Practice, The Records Management NHS Code of Practice and The Freedom of Information Act 2000.
2. Data collected within this project will be shared in the wider research community to

assist in the expansion of knowledge of the relationship between genotypes and phenotypes in intellectual disability. However, all data sharing will be pseudoanonymised and full sharing will only occur with ethically approved studies that have been reviewed and accepted by the management team.

3. Samples (blood saliva or hair roots) that are taken during the course of the project at the face-to-face interviews will be with full informed consent and will be pseudoanonymised and placed in a repository that is fully compliant with the Human Tissue Act legislation. For samples taken at face-to-face assessments by staff from Cardiff University, these will be stored within the National Centre for Mental Health (NCMH) research tissue bank. For all other samples these will be stored in a Human Tissue Bank compliant with the Human Tissue Act in England. Analysis of samples will be within the University of Cardiff, University of Cambridge or University College London.

<u>Management of research ethics for this project:</u>

1. This project is innovative and novel. We are unaware of many studies who are trying to provide online research tools that are both safe, dynamic and appropriate to this client group of mainly parents of children with an intellectual disability. We hope and anticipate that within the study period we will have multiple interactions and guidance from the ethics committee to help with design and safe execution of this project. We have strong support for this project from the patient support groups who are aware of the resources on the internet, as many are internet chat room users and Facebook group users specific for their particular microdeletion syndrome group. We wish to facilitate parental involvement and respect the parental drive to use more contemporary media methods for data collection, but also are concerned that we provide appropriate safe guards to the data and confidentiality issues. We request a dynamic ethical approval process and learn from the Unique support group who have agreed to comment and critique our processes.
2. This current protocol covers recruitment using the Musketeers Memorandum for children under 16 and adults with capacity from England, Wales, Northern Ireland and Scotland and adults who lack capacity in England, Wales and Northern Ireland only.