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)
Genomics in the Investigation of Epilepsy (GenIE) Study

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 review bodies are you applying to?

- ☐ HRA Approval
- ☑ NHS/HSC Research and Development offices
- ☐ Social Care Research Ethics Committee
- ☑ Research Ethics Committee
- ☐ Confidentiality Advisory Group (CAG)
- ☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

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

◉ Yes ○ No

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

Please describe briefly the involvement of the student(s):
The main researcher is using this study as basis for a PhD degree

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

(●) 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

NHS Health Research Authority

Application to NHS/HSC Research Ethics Committee

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)
Genomics in the Investigation of Epilepsy (GenIE) Study

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

REC Name:
Scotalnd A Rec

REC Reference Number:
16/SS/0054

Submission date:
12/02/2016

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Can stratification of childhood epilepsy through detailed phenotyping and whole genome sequencing identify novel genetic aetiologies and genetic modifiers of treatment response?

A2-1. Educational projects

Name and contact details of student(s):

Student 1

	Title	Forename/Initials	Surname
	Doctor	Joseph	Symonds
Address	The Old Schoolhouse		
	Clachan of Campsie		
	East Dunbartonshire		
Post Code	G667AB		
E-mail	josephsymonds@nhs.net		
Telephone	07709198925		
Fax			

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
PhD

Name of educational establishment:
Glasgow University

Name and contact details of academic supervisor(s):

Academic supervisor 1

	Title	Forename/Initials	Surname
	Professor	Sameer	Zuberi
Address	Fraser of Allander Neurosciences Unit		
	Royal Hospital for Children		
	1345 Govan Road		
Post Code	G514TF		
E-mail	sameer.zuberi@nhs.net		
Telephone	01414526685		
Fax			

Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	**Academic supervisor(s)**
Student 1 Doctor Joseph Symonds	☑ Professor Sameer Zuberi

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- ○ Student
- ◉ Academic supervisor
- ○ Other

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Sameer	Zuberi
Post	Research Fellow		
Qualifications	MbChB, MD, FRCP, FRCPCH		
Employer	NHS		
Work Address	Fraser of Allander Neurosciences Unit		
	Royal Hospital for Children		
	New South Glasgow University Hospitals		
Post Code	G514TF		

Work E-mail	josephsymonds@nhs.net
* Personal E-mail	josephsymonds@nhs.net
Work Telephone	07709198925
* Personal Telephone/Mobile	07709198925
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
Ms	Leigh	Hamilton

Address	New South Glasgow University Hospital 1345 Govan Road
Post Code	G514TF
E-mail	Leigh.Hamilton@ggc.scot.nhs.uk
Telephone	
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):	YRSS/CRF(E)/2015 01
Sponsor's/protocol number:	GN15NE178
Protocol Version:	
Protocol Date:	
Funder's reference number:	
Project website:	

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. 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.

Genetic and Autoimmune Childhood Epilepsy (GACE) Study - IRAS number 135019

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.*

Background:
Epilepsy is the commonest serious neurological disease, affecting 50-60 million people worldwide. Approximately 60% of all epilepsy is primarily genetic in nature. More than 500 different genes have now been identified as important in the causation of epilepsy.
The recent advance of genetic technology now offers the benefits of genetic diagnosis to many families for whom this had previously not been possible. Benefits of genetic diagnosis include offering an explanation for the epilepsy, counselling for recurrence risk in future offspring, and guidance on prognosis. In some cases genetic diagnosis informs epilepsy treatment choice.
Epilepsy can be very difficult to treat. For one third of patients with epilepsy the condition is resistant to treatment, or "refractory". A "personalised medicine" approach, where treatment is tailored to the genetic makeup to the individual, may help reduce this proportion of refractory cases, and improve outcomes.

Aims:
1. To investigate whether the application of Next Generation Sequencing (NGS) technology, including gene panels, Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS), combined with detailed phenotyping, can be used to find new genetic aetiologies for epilepsy
2. To investigate whether NGS can be used to identify meaningful genetic modifiers for treatment response in patients with genetic epilepsy

Methods:
This project will involve doing NGS,including WGS, on i) Patients and their parents (trios) with presumed genetic epilepsy, or a developmental disorder known to be associated with epileptic seizures, to identify new genetic causes of epilepsy; and ii) Patients with pathogenic SCN1A mutations to identify genetic markers of treatment response. Recruitment will be from a cohort of patients referred to the West of Scotland epilepsy genetics service. Suitable participants will be identified from the service's existing database. Detailed phenotypic information on each case will be obtained.

Analysis:
Analysis of variants found and ascertainment of their bio-functional consequences will take place in the genetics laboratory in Glasgow, and also in laboratories with whom we have a research agreement, including the Wellcome Trust Centre for Human Genetics (WTCHG) based at Oxford University. Whole Genome Sequencing, where performed, will be done at the WTCHG.

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, R&D office 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.

Consent issues:

It is important that all patients participating in clinical studies are fully informed about the nature of the research. Participation must not be under any duress. There must not be any real or perceived penalties for not participating, nor any bribery used to encourage participation.

Before consent is taken for genetic testing to be performed on DNA samples, research participants will be given verbal

and written information about what the research involves, including what results they may be informed of.
This project will involve recruitment of children under the age of 16 years, and may also involve some adults with learning disability. Special provisions need to be made for consenting in these cases. Parents will be able to give consent for children under the age of 16 years who are deemed unable to consent for themselves. Consent from either parent will be accepted, provided they have legal guardianship. In cases where consent is taken on behalf of children from parents, assent from the child will be sought(1). In cases where adults with learning disability are recruited, the Adults with Incapacity (Scotland) Act will be adhered to. This requires that consent should be obtained from any guardian or welfare attorney who has the power to consent to the adult's participation in research or, if there is no such guardian or welfare attorney, from the person's nearest relative. A separate adults with incapacity consent form will be used.As the law for adults with incapacity is different in other countries, we will not be recruiting any participants over the age of 16 from outwith Scotland.
In order to allow accurate interpretation of genetic data from DNA samples from the "probands" (patients affected by epilepsy), parental DNA samples will also be required. Separate consent forms will be created for this purpose. Individual consent will be taken from each biological parent.

Reporting of results:

Previous research has demonstrated that participants in epilepsy genetic research want to be told about the genetic findings, regardless if this has any implications for treatment, prognosis, or recurrence risk(2). All positive genetic findings that are thought likely to explain part or all of the patient's epilepsy or treatment response, will be reported back to the family and discussed fully at a clinic appointment with the patient's epilepsy doctor. Patients will also be offered an epilepsy genetic clinic appointment in Glasgow. This is a dedicated clinic with clinical geneticist and epilepsy specialist. If attendance at this clinic is wanted, but is not possible the referring clinician will be advised to request a local clinical genetics meeting. In all cases we will suggest validating research findings in a local laboratory with Clinical Pathology Accreditation (CPA).

Incidental findings:

The analysis of whole genomes brings with it the potential for the discovery of one or more of many incidental findings. In this case we mean the identification of a pathogenic (disease causing) mutation in a gene that is not related to epilepsy or neurodevelopmental disorders. In this study analysis and reporting of genetic data not thought to be relevant to the study subject will not take place. As part of the consenting process families will be made fully aware that, though WGS has the potential to look at all human DNA, only genetic findings relevant to epilepsy and neurodevelopmental disorders will be reported.

Data protection and anonymity:

Due to the size of the genomic data obtained from WGS, it will not be possible to store this data on NHS computers. The WTCHG has large servers that will be used for the storage of WGS data. Such data will be fully anonymised and password-protected so that only people with the authority to do so can access the data. Any genomic data generated by laboratories other than WTCHG will also be full anonymised and password-protected. Any genetic or clinical data shared with collaborators in other research laboratories and institutions will also be fully anonymised. Correlation between the WGS data and any patient-identifiable information will only be possible by the Principal Investigator and the research team in Glasgow since only they will have access to the unanonymised details.

References:

(1) Wendler DS. Assent in paediatric research: theoretical and practical considerations. J Med Ethics 2006; 32(4):229-234.
(2) Shostak S, Zarhin D, Ottman R. What's at stake? Genetic information from the perspective of people with epilepsy and their family members. Soc Sci Med 2011;73(5):645-654.
(3) Ethical Advisory Group for the UK10 Project. Ethical governance framework. UK10K [online]. 2010; Available at: www.uk10k.org/assets/ef_uk10k_v21.pdf. Accessed 09/02, 2015.
(4) Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med 2013;15(7):565-574.

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

- [x] Cohort observation
- [ ] Controlled trial without randomisation
- [x] Cross-sectional study
- [ ] Database analysis
- [ ] Epidemiology
- [ ] Feasibility/ pilot study
- [x] Laboratory study
- [ ] Metanalysis
- [ ] Qualitative research
- [x] 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.*

Can we use the most up to date genetic testing techniques to identify new genetic causes of epilepsy, and identify genes that modify response to antiepileptic medication.

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

• Can we describe new epilepsy phenotypes (descriptions of disease) associated with genetic variants?
• Can we identify any clinical features that predict a particular genetic finding?
• How do families and clinicians find the process of next generation sequencing in epilepsy?.

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

Epilepsy is the commonest serious neurological condition, affecting 50-60 million people worldwide. Epilepsy can have numerous causes, but approximately 60% of all epilepsy is primarily genetic in nature. In the last 20 years many genes have been identified as important in the causation of epilepsy and with new genetic techniques the rate of discovery is increasing. Despite these advances the vast majority of people with a presumed genetic epilepsy still do not have a genetic diagnosis.

There are many therapeutic options for epilepsy however in approximately one third of cases, epilepsy is drug resistant. Drug resistant epilepsy is defined as continuing epileptic seizures despite trials of treatment with appropriately chosen and adequately dosed anti-epileptic medications since long-term seizure remission after two drug failures is unlikely(1). Gaining a better understanding of the genetic factors that determine treatment response may help inform more personalised medication choice and reduce the proportion of refractory cases.
In many cases of epilepsy, the genetic causation is complex – the existence of the phenotype requiring a combination of mutations in two or more susceptibility genes, possibly together with environmental influences. However, in cases where the phenotype is more severe it is more likely that a single gene de novo variant largely explains the phenotype. Examples of such phenotypes include early onset epilepsy; epilepsy with encephalopathy; or epilepsy with comborbid developmental impairment, movement disorder or autism spectrum disorder. Such epilepsies are often referred to as “monogenic” epilepsies.

A good example of a monogenic epilepsy is Dravet syndrome. Dravet syndrome is characterised by onset of seizures in the first year of life in an otherwise healthy infant. Initial seizures are typically febrile hemiclonic seizures. There is progression to involve other seizure types and developmental stagnation or regression is seen. 60-80% of Dravet syndrome is caused by mutations in the SCN1A gene, and in small proportions mutations in various other genes have been identified. Despite Dravet syndrome being a well-characterised monogenic epilepsy, in 20-30% of cases a genetic diagnosis cannot be made(2).The implication is therefore that other Dravet syndrome genes remain to be discovered.

Another group of epilepsies that has been found to have a strong monogenic influence is Early Infantile Epileptic Encephalopathy (EIEE). At least 45 different genes have been implicated in EIEE, yet when Whole Exome Sequencing (WES) techniques have been used to look for genetic causes in of EIEE, the majority of cases remain undiagnosed.

The Epi4k study recruited 264 patients with EIEE and performed WES. In only 26 (10%) cases was a pathogenic variant identified(3). In EIEE the use Whole Genome Sequencing (WGS) has been shown to deliver higher genetic diagnosis rates than WES, but this has only been demonstrated on a small number of patients(4). To permit meaningful interpretation of WES or WGS data, highly detailed phenotypic information is required(5). This project, unlike previous WES or WGS studies will have access to detailed phenotyping.

Benefits of genetic diagnosis include offering an explanation for the epilepsy, counselling for recurrence risk in future offspring, and guidance on prognosis. In some cases genetic diagnosis informs epilepsy treatment choice: for example it has been demonstrated that knowledge of an SCN1A mutation tends to steer clinicians away from using sodium channel-blocking medications such as Carbamazepine and Lamotrigine since in general it has been observed that these medications worse seizure control(6). However, the full picture of the relationship between SCN1A mutations remains to be elucidated. Recently it has been demonstrated that some Dravet syndrome patients with SCN1A mutations can have a good response to Lamotrigine and a significant deterioration when Lamotrigine is withdrawn(7).

In summary the two key scientific justifications for this research are as follows:

1.So far one study involving 6 cases of EIEE has demonstrated that WGS can achieve high rates of genetic diagnosis. This has yet to be tested on a larger scale and with non EIEE patients. We aim to investigate whether novel genetic causes of epilepsy can be identified through in deep phenotyping and WGS

2.Little is known about the factors that modify treatment response in monogenic epilepsy. We aim to investigate whether WGS can be used to identify genetic markers of response to sodium-channel blocking medications.

References:
(1) Berg AT, Levy SR, Testa FM, D'Souza R. Remission of epilepsy after two drug failures in children: a prospective study. Ann Neurol 2009;65(5):510-519.
(2) Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135(Pt 8):2329-2336.
(3) Epi4K Consortium. Epilepsy Phenome/Genome Project. Allen AS. Berkovic SF. Cossette P. Delanty N. Dlugos D. Eichler EE. Epstein MP. Glauser T. Goldstein DB. Han Y. Heinzen EL. Hitomi Y. Howell KB. Johnson MR. Kuzniecky R. Lowenstein DH. Lu YF. Madou MR. Marson AG. Mefford HC. Esmaeeli Nieh S. O'Brien TJ. Ottman R. Petrovski S. Poduri A. Ruzzo EK. Scheffer IE. Sherr EH. Yuskaitis CJ. Abou-Khalil B. Alldredge BK. Bautista JF. Berkovic SF. Boro A. Cascino GD. Consalvo D. Crumrine P. Devinsky O. Dlugos D. Epstein MP. Fiol M. Fountain NB. French J. Friedman D. Geller EB. Glauser T. Glynn S. Haut SR. Hayward J. Helmers SL. Joshi S. Kanner A. Kirsch HE. Knowlton RC. Kossoff EH. Kuperman R. Kuzniecky R. Lowenstein DH. McGuire SM. Motika PV. Novotny EJ. Ottman R. Paolicchi JM. Parent JM. Park K. Poduri A. Scheffer IE. Shellhaas RA. Sherr EH. Shih JJ. Singh R. Sirven J. Smith MC. Sullivan J. Lin Thio L. Venkat A. Vining EP. Von Allmen GK. Weisenberg JL. Widdess-Walsh P. Winawer MR. De novo mutations in epileptic encephalopathies. Nature 2013;501(7466):217-221.
(4) Martin HC, Kim GE, Pagnamenta AT, Murakami Y, Carvill GL, Meyer E, et al. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. Hum Mol Genet 2014;23(12):3200-3211.
(5) Mina ED, Ciccone R, Brustia F, Bayindir B, Limongelli I, Vetro A, et al. Improving molecular diagnosis in epilepsy by a dedicated high-throughput sequencing platform. Eur J Hum Genet 2015 print;23(3):354-362.
(6) Brunklaus A, Dorris L, Ellis R, Reavey E, Lee E, Forbes G, et al. The clinical utility of an SCN1A genetic diagnosis in infantile-onset epilepsy. Dev Med Child Neurol 2013;55(2):154-161.
(7) Dalic L, Mullen SA, Roulet Perez E, Scheffer I. Lamotrigine can be beneficial in patients with Dravet syndrome. Dev Med Child Neurol 2015;57(2):200-202.

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.*

Methods:

Subjects:

Once informed consent from all participants or their parents/guardians has been obtained, NGS will be performed on the following:

1.At least 50 patients with childhood-onset epilepsy and distinctive phenotypes, such as comorbid movement disorder , for whom thusfar no genetic diagnosis has been made. Their parents will be recruited concomitantly in order for trio analysis to be performed. If in the course of this research we identify new genes associated with particular phenotypes, efforts will be made to recruit more patients with the same phenotype sot that the genetic findings can be

further validated.

2.At least 50 patients with childhood-onset epilepsy and confirmed pathogenic SCNIA mutations
o At least 25 will have previously demonstrated a positive response to a sodium channel-blocking AED (Lamotrigine, Carbamazepine, Phenytoin or Lacosamide)
o At least 25 will have previously demonstrated a negative response to a sodium channel-blocking AED (Lamotrigine or Carbamazepine, Phenytoin or Lacosamide)

Recruitment:
Patients will be recruited through the referring/managing clinician (Paediatrician or Neurologist) for all cases.

The following databases will be used for case identification:

1.The existing west of Scotland epilepsy genetics service database of all patients referred since 2004 for clinical genetic testing. Childhood Epileptic Encephalopathies Research Database - quoted in GACE. The database contains phenotypic information on each case, which was obtained from the referring clinician at the point of referral. Each referring clinician was asked to complete a structured referral form including the following details: semiology of the first seizure; subsequent seizure types; findings on electroencephalogram (EEG) and neuroimaging (MRI or CT brain scan); any comorbid movement disorder; any developmental delay or regression; any comorbid autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD); any medications that have been associated with a worsening in seizure control worse; and any medications that have been associated with an improvement in seizure-control. The database gives details as to whether families have given consent for further genetic testing or contact.

2.Patients already enrolled and consented for participation in the GACE study (IRAS ID 135019). The GACE study involves NGS panel testing of about 100 epilepsy-related genes in children presenting under the age of 3 years with new onset epilepsy or with complex febrile convulsions. The consent process for enrolment in GACE includes taking consent for more complex genetic testing to be performed on samples, if and when available.

3.Offering families the opportunity to take part via the charity Dravet Syndrome UK (#1128289). Dravet Syndrome UK will be asked to circulate a flyer about this project. Through the details provided on the flyer families will be able to ask their managing clinician to recruit them to the study. Alternatively families will be able register their interest directly to Dravet Syndrome UK who will then ask them to provide details of the managing clinician, who will then be contacted about the project by the research team.

In order to recruit both SCN1A patients who have improved with sodium-channel blocking medication and those who have deteriorated with sodium-channel blocking medication, questionnaires will be sent to families (via Dravet syndrome UK) and clinicians (via existing Scottish Networks) in order to capture what response was had to these medications.

When a suitable participant has been identified through any of these routes, the participant's managing clinician will be contacted, given information on the study, and asked if appropriate to consider inviting the patient to take part in the study. If a family expresses interest they will then be invited to attend a research clinic. A member of the research team can offer to see the families in their local hospital or in Glasgow. Reasonable travel expenses will be offered to families. Prior to the clinic appointment families will be sent written information on the study.

If families are interested in taking part, consent will be obtained at the research clinic for the following:

• NGS panel of c.100 genes, to be done in Glasgow, if not already done
• WGS, to be done in Oxford
• Storage of anonymised data on a dedicated secure server
• Sharing of anonymised genetic data with research collaborators
• Further contact in case further detailed information about the case is required
• Further contact in case additional sampling such as skin biopsy, is desired for functional analysis of variants
• Questionnaires to be offered, enquiring about their experience of the testing process
• Contact with other health care providers such as the GP and paediatrician, to share clinically relevant information
• Sharing or results relevant to epilepsy and neurodevelopmental disorders
• No-sharing of incidental findings not relevant to epilepsy or neurodevelopmental disorders

We aim to recruit the following two groups of patients:-
• Patients with epilepsy and distinctive phenotypes. Genetic testing will be done offered to the patient and both biological parents (trios).
• SCN1A-¬positive patients who have at some time demonstrated an improvement in seizure control with sodium channel-blocking AEDs
• SCN1A-¬positive patients who have at some time demonstrated a worsening of seizure control with sodium

channel-blocking AEDs.

Clinical assessment:

All index cases will undergo detailed clinical assessment. Clinical assessment will be carried out at a dedicated clinic at the Royal Hospital for Children, Glasgow. For any cases recruited from out-with Glasgow, a member of the research team will be able travel to the family's local hospital to undertake the assessment there. Clinical assessment will involve a detailed history, including all previous medications tried and responses to these; physical examination; and collation of existing investigation results such as EEG and neuroimaging. Most phenotypic data will come from our specialist referral forms, review of case notes, and questionnaires to managing physician. Regular clinic visits will be arranged if additional data and follow-up data are required.

Consent:

Because of the implications of WGS and potential for incidental findings, all families taking part in the study will undergo pre-test counseling. Fully informed signed consent will be obtained from all family members undergoing WGS testing prior to samples being sent to WTCHG and tested. Families will also be asked to give consent for anonymized genetic data with be shared with laboratories with whom we have a research agreement. It is envisaged that this research may benefit from further samples being taken once genetic variants have been identified. Some sophisticated functional analyses of genetic variants can be performed on cultures fibroblasts obtained by skin biopsy. Families will be asked to give consent if they are happy to be contacted in future for such investigations.

Testing protocol:

The c.100 gene NGS panel will be based at the Glasgow Epilepsy genetics service.

WGS and bioinformatic analysis will initially be carried out at the WTCHG in Oxford, under the supervision of Dr. Houman Ashfrafian. In future WGS may take place at other laboratories with whom we have a research agreement. Any laboratory undertaking this will only have access to anonymised samples and must have a rigorous data security policy.

Functional analysis of gene variants on anonymised data may be carried out at a number of laboratories with whom we have a research agreement.

Analysis:

Bioinformatic analysis:

Bioinformatic analysis of WGS data will be carried out at the Wellcome Trust Centre for Human Genetics (WTCHG) in Oxford under the supervision of Professor Houman Ashrafian. Anonymised genomic data may be sent to collaborators in other laboratories. Examples of collaborative data sharing projects include the Decipher database and the Belgian SCN1A database. Genetic variants are typically available in public databases to allow labs around the world to share data to inform testing. We may share details of anonymised variants with groups in whom we have a formal research agreement.

Dissemination of results:

The project will be written up as a PhD thesis. All relevant genetic findings will be made publically available. Findings will be shared through presentations to academic meetings, presentations to family groups, and presentations to neurology and epilepsy groups such as Scottish Paediatric Epilepsy Network (SPEN), Scottish Epilepsy Group (SEG), British Paediatric Neurology Association (BPNA), and International League Against Epilepsy (ILAE). All findings academic interest will be submitted for publication in peer-reviewed journals. The Research Fellow will establish the appropriate ethical framework and consents so that the individuals referred to the Glasgow Epilepsy Genetics Service who test negative for known genes can be enrolled in future local, national and international collaborative studies to identify new genetic causes of epilepsy.

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
- [ ] Management of the research
- [x] Undertaking the research

☐ Analysis of results

☑ Dissemination of findings

☐ None of the above

Give details of involvement, or if none please justify the absence of involvement.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

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

Patients must have epilepsy, or a developmental disorder in which epilepsy is commonly associated.

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

Patients without epilepsy or an epilepsy-associated neurodevelopmental disorder will not be included in the study. Patients over the age of 16 residing outwith Scotland will not be included.

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
Signing of consent, having been given verbal and written information about the study.	1	0	30 minutes	Research Fellow, at Royal Hospital for Children, Glasgow, or health care facility local to the family
Clinical history taking to clarify phenotype	1	0	90 minutes	Research Fellow, at Royal Hospital for Children, Glasgow, or health care facility local to the family
Pre-testing questionnaire	1	0	30 minutes	Parent/gaurdian, at their convenience
Feedback of results	1	0	30 minutes	Principal Investigator or patients epilepsy doctor, at Royal Hospital for Children, Glasgow, or health care facility local to the family
Post-testing questionnaire	1	0	30 minutes	Parent/gaurdian, at their convenience

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
Blood sampling (only in cases where sufficient quality DNA not already available in Glasgow laboratory)	1	0	10 minutes	Research Fellow, at Royal Hospital for Children, Glasgow, or health care facility local to the family
Skin biopsy (only in cases where a genetic variant for which analysis through functional work on cultured fibroblasts is desired) and where consent has been given	1	0	10 minutes	Research Fellow, at Royal Hospital for Children, Glasgow, or health care facility local to the family

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

4 years

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.

If extra blood sampling is required there may be some temporary discomfort for the subjects. This will be minimised by using appropriate analgesia such as oral sucrose (for neonates), cold spray, or local anaesthetic cream such as Emla® or Ametop®. All efforts will be taken to identify whether existing samples are already available in the laboratory so additional sampling is only undertaken where absolutely unavoidable. If patients are likely to be getting other, clinically indicated, blood tests within the time frame of the study attempts will be made to coincide sampling so that no additional venepucture is undertaken. For any patients undergoing skin biopsy, all efforts will be made to coincide this procedure with other, clinically indicated procedure that will be taking place under anaesthetic.

There may be inconvenience involved in attending additional clinics in order to go through consenting and additional history taking. This will be minimised by arranging clinic appointments locally to the patient wherever possible, and a time that is convenient for the family.

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

The majority of people affected by familial epilepsy respond positively when offered genetic testing. Qualitative research looking into why this is has identified that having knowledge of an underlying cause gives patients strength to face their epilepsy, more confidence to advocate for others with the same illness, and reduces feelings of self-blame(1,2). Brunklaus et al. found that 87% of 182 carers who had a child test positive for SCN1A mutation reported that the genetic result was helpful in giving an explanation for the epilepsy(3).
Medical research participants also often feel a sense of reward for contributing to the scientific advance of a field that is important to them.

(1) Hammond CL, Thomas RH, Rees MI, Kerr MP, Rapport F. Implications for families of advances in understanding the genetic basis of epilepsy. Seizure 2010;19(10):675-679.
(2) Shostak S, Zarhin D, Ottman R. What's at stake? Genetic information from the perspective of people with epilepsy and their family members. Soc Sci Med 2011;73(5):645-654.
(3) Brunklaus A, Dorris L, Ellis R, Reavey E, Lee E, Forbes G, et al. The clinical utility of an SCN1A genetic diagnosis in infantile-onset epilepsy. Dev Med Child Neurol 2013;55(2):154-161.

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).*

The existing West of Scotland epilepsy genetics database will be the primary means by which participants will be identified. This is a non-anonymised database and it includes all patients that have been referred to the service for clinical genetic testing, as well as patients who have been enrolled in the GACE study. A certain amount of phenotypic information is input into the database and in many cases it is anticipated that this will be sufficient to identify suitable participants for the study. Interrogation of the database will be undertaken by the research fellow. It is anticipated that some suitable participants will not be identifiable through interrogation of the database alone. Therefore the research fellow will also use existing national clinician networks including the Scottish Paediatric Neurology Group (SPNG) and Scottish Paediatric Epilepsy Network (SPEN) to create a forum with paediatric neurologists and geneticists across Scotland through which suitable participants can be identified and identified to take part in the research. As part of the case selection process, the research fellow will use the access that he already has, as an NHS clinician with NHS Greater Glasgow and Clyde, to review electronic case records and obtain more detailed phenotypic information. In some cases historical paper records will be requested. Where the research team requires access to clinical notes from health boards outwith NHS Greater Glasgow and Clyde, existing policies at NHS trusts will be adhered to. These may require members of the research team to obtain Research Passports.

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:
Clinical notes of patients will be reviewed in detail by the Research Fellow, but only after consent has been obtained.

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

◉ Yes ○ No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

◉ Yes ○ No

If Yes, please give details below.
The consent process will involve obtaining consent for the Research Fellow to review medical records of the participants.

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).
We will ask the charity Dravet Syndrome UK to place a link to our study website on their website. Our study website will make it clear that all recruitment to the study must be through the patient's managing clinician. Therefore there will be no direct recruitment through posters, leaflets, adverts or websites.

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

There will be only one avenue through which participants will be first approached. This will be via the patient's managing clinician. The managing clinician will be either a paediatrician with a specialist interest in neurology, a paediatric neurologist or an adult neurologist. Once the research team has identified potential a suitable participant

from the West of Scotland epilepsy genetics database he will write to/email that patient's lead epilepsy clinician and enquire whether he or she would be happy to discuss participation in the research with the family. All clinicians who could potentially be looking after suitable research participants will be provided with information leaflets about the study that they can give to the families. On these information leaflets will be contact details for the research team so that the families can then make contact with the research team about they study – to book an appointment to discuss consent, or to ask any further questions. The managing clinician will also be able to go through consent with families and complete the consent forms with them.

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.

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

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

A minimum of 24 hours.

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?

Many of the participants in this study will have been recruited to previous genetic research studies. Most of the patients with SCN1A mutations will have been involved in various studies assessing their epilepsy phenotype, learning and behaviour, and family quality of life. Some of the patients without any as yet known causative genetic mutations will have undergone genetic testing in Glasgow and elsewhere as part of research studies such as the Genetic and Autoimmune Childhood Epilepsy (GACE) study Deciphering Developmental Disorders (DDD) study.

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 use of interpretation services will be employed, where needed.

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?

N/A

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:

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)*

- ☑ 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
- ☐ 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
- ☐ Storage of personal data on any of the following:
  - ☐ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☑ Private company computers
  - ☐ Laptop computers

Further details:
Fully anonymised data may be stored on private company computers in order to make use of "cloud storage" facilities.

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.*

All data not stored on NHS or Glasgow University password protected computers will be fully anonymised.

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.*

The Research Fellow, in consultation with the patient's lead epilepsy clinician, once having obtained consent, will need to review electronic and paper records, as well as record history taking and examination findings taken as part of the study. Research passports will be obtained where required by local NHS R&D.

Storage and use of data after the end of the study

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:
Data will take >12 months to fully analyse.

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.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

(●) Yes ( ) No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

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

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. 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.

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:*

- [x] Peer reviewed scientific journals
- [x] Internal report
- [x] Conference presentation
- [x] 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
- [x] Other (please specify)

Feedback to parent groups and voluntary organisations

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.

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
- [x] 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:
Funding for this project was obtained through a successful application to the Yorkhill Research Support Scheme (YRSS, AMRC accredited). The reward process involved scrutiny of the project's methodology by external peer reviewers, none of whom had previously done any collaborative work with the Principal Investigator, followed by a formal interview of the Research Fellow by paediatric academics from the West of Scotland.

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
- [ ] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [x] 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

Department
Institution
Work Address

Post Code
Telephone
Fax
Mobile
E-mail

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

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

- Number of new genes found
- Number of genetic associations with medication response found
- Novel phenotypes reported with known genes

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

• Patient and family satisfaction with the process of NGS
• Clinician satisfaction with the process of NGS

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: 200
Total international sample size (including UK):
Total in European Economic Area:

Further details:
• At least 25 patients with SCN1A mutations and worsening of symptoms with sodium channel blocking medication
• At least 25 patients with SCN1A mutations and improvement of symptoms with sodium channel blocking medication
• At least 50 patients and the parents (150 total) with epilepsy and interesting or novel phenotypes and no existing genetic diagnosis

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.*

Based on previous published sample sizes used when identifying new genetic variants in childhood epilepsy

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.

Each individual is expected to harbour approximately 70 de novo mutations (variants in their genome that have not been inherited from either parent). Analysis of genomes involves ascertaining which, if any of these are clinically relevant or “pathogenic”. Bioinformatic analysis of variants found through whole genome sequencing makes use of a wide range of techniques to ascribe pathogenicity to mutations. These techniques include identifying variants that alter amino acid sequence, particularly those that significantly alter protein structure or function, and identifying variants in DNA sequence that is typically highly conserved across species. Recurrent involvement of a particular gene or part of the genome in patients with similar phenotypes also lends weight to interpretation of findings.
For analysis of some of the qualitative aspects of the work, such as patients and clinician perceptions of WGS, grounded theory techniques will be used.

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

Post
Qualifications
Employer
Work Address

Post Code
Telephone
Fax
Mobile
Work Email

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:

If Other, please specify:

Contact person

Name of organisation	NHS Greater Glasgow & Clyde
Given name	Paul
Family name	Dearie
Address	West Glasgow Ambulatory Care Hospital
Town/city	Glasgow
Post code	G3 8SW
Country	UNITED KINGDOM
Telephone	01412321810
Fax	
E-mail	Paul.Dearie@ggc.scot.nhs.uk

Is the sponsor based outside the UK?

( ) Yes (●) No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

☑ 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	Yorkhill Research Support Scheme
Address	New South Glasgow University Hospital
	1345 Govan Road
	Glasgow
Post Code	G514TF
Telephone	
Fax	
Mobile	
Email	Jillian.Bryce@glasgow.ac.uk

Funding Application Status: ◉ Secured ◯ In progress

Amount:

Duration

Years: 3

Months: 0

If applicable, please specify the programme/ funding stream:

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

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
	Dr	Paul	Dearie
Organisation	NHS Greater Glasgow and Clyde Research and Development		
Address	West Glasgow Ambulatory Care Hospital Glasgow		
Post Code	G3 8SW		
Work Email	Paul.Dearie@ggc.scot.nhs.uk		
Telephone	01412321820		
Fax			
Mobile			

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

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

Planned start date: 05/08/2015
Planned end date: 06/08/2019
Total duration:
Years: 4 Months: 0 Days: 2

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)

Last result presented to the last patient/family in the study.

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

- [x] England
- [x] Scotland
- [x] Wales
- [x] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study

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:*

- [x] NHS organisations in England
- [x] NHS organisations in Wales
- [x] NHS organisations in Scotland
- [x] 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)
☐ 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: 0

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)

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)

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.

- [x] 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)

Please enclose a copy of relevant documents.

Part B: Section 4 – Use of residual or existing stored human tissue(or other human biological materials)

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

Blood or saliva
Skin biopsy

2. Will the samples be released to the researcher:

In fully anonymised form? *(link to stored tissue and data is broken)*
○ Yes ◉ No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*
○ Yes ◉ No

In a form in which the donor could be identifiable to researchers?
◉ Yes ○ No

If Yes, please justify.
Interpretation of genetic results is dependent on comprehensive evaluation of the phenotype

3. Has consent been obtained previously to use the samples for research

○ Consent has been given for all samples
◉ Consent has been given for some of the samples
○ No consent has been given

4. Please outline what consents are already in place, distinguishing between different groups of samples where appropriate.

Some parents/guardians have already given consent for additional genetic testing to be performed on samples that the Glasgow laboratory have. Nontheless additional specific consent for this study will still be obtained from these cases.

5. Is it proposed to seek further consent to use the samples in this research?

◉ Yes ○ No

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

Next Generation sequencing panel
Whole Genome Sequencing
Functional analysis of genetic variants (may involve skin biopsy)

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

(●) Yes ( ) No

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

(●) Yes ( ) No

11. 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.

Relevant genetic findings will be fed back to participants and their m=families via the managing clinician.

12. Who is the holder of the samples?

Please tick either/both boxes as applicable.

[x] NHS pathology department(s) / diagnostic archive(s)
Specific details of each department/archive are not required

[ ] Other research tissue bank(s) or sample collection(s)
Please provide further details of each bank/collection below

13. Will any of the samples be imported from outside the UK?

( ) Yes (●) No

14. Please give details of where the samples will be stored, who will have access and the custodial arrangements.

During the research period samples will be stored either at the West of Scotland clinical genetics laboratory, or at the Wellcome Trust Centre for Human Genetics in Oxford under the custody of Professor Houman Ashrafian.

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

[ ] Return to current holder of the samples
[x] Transfer to another tissue bank

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

[x] 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.)

[x] Storage by research team as part of a new research tissue bank

(The institution will require a storage licence for research 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 Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

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?

Blood or saliva
Skin biopsy

2. Who will collect the samples?

The Research Fellow

3. Who will the samples be removed from?

- [x] 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

In a form in which the donor could be identifiable to researchers?
(●) Yes ( ) No

If Yes, please justify.
Interpretation of genetic findings is dependent on comprehensive phenotypic analysis.

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

Next Generation sequencing panel
Whole Genome Sequencing
Functional analysis of genetic variants

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.

If significant genomic findings are made, the family will be invited to a clinic with a consultant clinical geneticist and genetic counsellor to discuss the findings and their implications.

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

During the research period WGS samples will be stored at the Wellcome Trust Centre for Human Genetics in Oxford under the custody of Professor Houman Ashrafian.

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:

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.

Learning Disability

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.

Participants with incapacity will only be recruited from Scotland.

Patients with the most severe forms of epilepsy typically have moderate to severe learning disability. Patients with both epilepsy and learning disability are more likely to have a genetic cause than patients with just epilepsy.
One of the aims of our study is to identify new genetic causes of epilepsy, without involving participants with moderate to severe learning disability we would be limited in this scope.

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?

The research fellow will decide whether patients have the capacity to consent. The research fellow has attended a number of courses on research standards and ethics. The research fellow also does a regular epilepsy clinic in which many of the patients have moderate to severe learning disability.

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.

The research may identify new genetic causes of these patients' epilepsy. Knowledge of a genetic cause has been shown to improve family quality of life in other studies, and may guide treatment strategy.

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:

For all new genetic causes of epilepsy found in this study the associated phenotype will be published in the medical literature. This will mean that other clinicians may be able to identify the same phenotype and request directed genetic testing in the future.

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?

No adults with incapacity to consent will be recruited from England and Wales

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.

No adults with incapacity to consent will be recruited from England and Wales

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?

A specific adults with incapacity consent form has been produced and this must be signed by the patient's welfare guardian before they can be recruited into the study.

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.

Questions B7-2 and B8-2 apply to any participants recruited in Northern Ireland.

B7-2. What arrangements will be made to consult, and seek assent from, a close relative or other person able to advise on the inclusion of the participant and on their presumed wishes and feelings?

No adults with incapacity to consent will be recruited from Northern Ireland

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.

B8-2. Is it possible that a participant might need to be treated urgently as part of the research before it is possible to seek assent from a close relative or other person?

○ 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 assent from a close relative or other person as soon as practicable thereafter.

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

Any significant results from the genetic investigations will be fed back to the patient's welfare guardian wither by their managing clinician, or at a genetic epilepsy clinic in Glasgow Royal Hospital for Children.

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?

Information sheets on the research will be given to the welfare guardian(s) of the each participant. The welfare guardian will be advised to share information as appropriate to the level of understanding of the participant.

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

No

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

If the welfare guardian wishes withdrawal at any stage, then the participant will be removed from the study and all data relating to them will be destroyed.

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).

We will aim to coincide any blood or tissue sampling with samples that are already being taken for clinical purposes. Where participants clearly object to blood or tissue sampling the welfare guardian will be asked if they would like to defer or abandon sampling.

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?

Welfare guardians will be asked if the participant mad made any advanced decisions and we will respect any such decisions completely in this research.

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.

0-16 years.
this is a study into genetic causes of epilepsy of onset in childhood.

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

no

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.

Consent will be obtained from parents or legal guardians where participants under the age of 16 do not have the capacity to consent for themselves.

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.

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 NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Research site		Investigator/ Collaborator/ Contact	
Institution name	NHS Greater Glasgow and Clyde	Title	Professor
Department name		First name/ Initials	Sameer
Street address	1345 Govan Road	Surname	Zuberi
Town/city	Glasgow		
Post Code	G514TF		
Institution name		Title	
Department name		First name/ Initials	
Street address		Surname	
Town/city			
Post Code			

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

3. 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.

4. 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.

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

6. 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.

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

8. 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 1998.

9. 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.

10. 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 1998.

11. 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 below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

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

NRES 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 Dr Sameer Zuberi on 05/03/2016 15:00.

Job Title/Post:	Consultant Paediatric Neurologist
Organisation:	NHS Greater Glasgow & Clyde
Email:	sameer.zuberi@nhs.net

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 duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken 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 Mr Paul Dearie on 09/03/2016 12:39.

Job Title/Post:	Research Coordinator
Organisation:	NHS Greater Glasgow and Clyde
Email:	paul.dearie@ggc.scot.nhs.uk

D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Dr Sameer Zuberi on 05/03/2016 14:58.

Job Title/Post:	Consultant Paediatric Neurologist
Organisation:	NHS Greater Glasgow & Clyde
Email:	sameer.zuberi@nhs.net