BRITISH PAEDIATRIC NEUROLOGY SURVEILLANCE UNIT

Application Form

Please use the space provided to complete this form. Please read questions carefully as failure to provide sufficient detail may lead to a delay in processing the application or its rejection.

1) Title of study:

SCN1A Horizons. A natural history study of SCN1A-relatd epilepsies in the United Kingdom

2) Investigators (Indicate Principal Investigator)

Please list all investigators involved in the study, their job title, affiliation, and contribution to this study. Please also indicate clearly the principal contact for correspondence on this application, giving a full contact address, email address and telephone number. (If more than four, please insert an additional row).

	Principal investigator: name and contact details	**Job title and affiliation**
1	Professor Andreas Brunklaus	Consultant Paediatric Neurologist – Royal Hospital for Sick Children, NHS Greater Glasgow & Clyde
	Additional investigators: names	
2	Professor Liam Dorris	Consultant Paediatric Neuropsychologist – Royal Hospital for Sick Children, NHS Greater Glasgow & Clyde
3	Professor J Helen Cross	Consultant Paediatric Neuologist – Great Ormond Street Hospital, London
4	Professor Sameer M Zuberi	Consultant Paediatric Neurologist – Royal Hospital for Children, NHS Greater Glasgow & Clyde
5	Dr Elaine Hughes	Consultant Paediatric Neurologist, Guy's & St Thomas', London
6	Dr Michael Absoud	Consultant Paediatric Neurologist, Guy's & St Thomas', London
7	Professor Sanjay Sisodiya	Consultant Neurologist, University College London Hospitals NHS Foundation Trust

8	Dr Rhys Thomas	Consultant Neurologist, Newcastle Hospitals NHS Foundation Trust
9	Professor Mark Kelson	Senior Lecturer in Data Science, University of Exeter

3) Proposed starting date:

Proposed duration of study: 3 years (recruitment anticipated to be completed within 12 months with a further 24 months longitudinal follow-up)

Proposed territorial coverage:
Please tick one response.

UK and Ireland ☐ **UK only X** **Regional ☐ ……**

4) Case definition

Please give careful thought to providing a precise and practical definition (based on symptoms/signs/investigations) that will be understood by paediatric neurologists. Use an internationally accepted case definition if at all possible and reference previous studies if relevant.

Case definition: A child or adult with a diagnosis of epilepsy who has undergone genetic testing and has a confirmed pathogenic SCN1A variant.

Age range for cases: 0 months – adulthood

Inclusion criteria:

Patients meeting the following criteria will be considered eligible for this study:
1. Patient and/or legally authorised representative must be willing and able to give informed consent/assent for participation in the study.
2. Patient and their parent/caregiver are willing and able (in the Investigator's opinion) to comply with all study requirements (including ability and willingness to comply with virtual visits).
3. Participant has a confirmed pathogenic (class 5) or likely pathogenic (class 4) *SCN1A* variant, as demonstrated by genetic testing.

* Please note, patients participating in other research studies or trials may still take part in this study which does not administer any investigational medicinal products.

Exclusion criteria:
1. Patient has any other significant disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or may affect the patient's ability to participate in the study.

5) Expected Numbers

Please supply an estimate of the number of cases expected each year, i.e. yearly incidence rate. Provide a reference or an explanation for this estimate. Please also indicate the source of denominator data for calculating incidence.

Expected numbers (per year):

Estimated 40-60 new diagnoses per year.

This estimate is based on findings from a prospective, population-based national cohort which found SCN1A-related epilepsies in 1 per 12,200 births. Based on official figures released by the Office for National Statistics, the UK live birth rate was 681,560. This would equate to approximately 56 cases of SCN1A-related epilepsies.

Source of denominator data:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6658850/

https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/vitalstatisticspopulationandhealthreferencetables

6) Ethical approval

The majority of studies will require research ethics committee (REC) approval.

- If this is an audit study that does not require formal ethical approval, please forward to the BPNSU a copy of the confirmation from your REC that ethical approval is not needed.

- If this study does have ethical approval, then please forward a copy of the ethics application and a copy of the approval letter.

Ethical approval has been obtained.
Scotland REC reference – 22/SS/0072
England/Wales REC reference – 22/WA/0117
Amendment SA 03 included an amendment to allow for identification of participants via BPNSU (detail added to Protocol v2.0).

7) Research questions/surveillance objectives

Please indicate below the type of study that you are intending to undertake. **It should be noted that the BPNSU is only acting as a conduit between the investigator and anonymised cases. It does not provide any direct contact with patients**.

- Surveillance ☐
- Case Registry ☐
- Incidence or Prevalence study ☐
- Cohort study **X**
- Case-control Study ☐
- Interventional Study (e.g. therapeutic trial) ☐
- Audit ☐

8) Methods

Please provide clear details of the study methodology you intend to employ to answer your research questions. Please forward a copy of your study protocol and/or COREC form with this application form.

We will systematically collect longitudinal validated outcome measures for *SCN1A* variant-carrying patients across the UK. This will be done ensuring that data collected are not only clinically meaningful, but also sufficiently robust for use in clinical research. We will benefit from the uniformity of assessment that having a single UK National Health Service (NHS) allows.

The study participants will have two different types of standardized assessments: a clinical standard of care assessment and a neuropsychology assessment. Clinical assessments will be conducted 6-monthly as part of the patient's routine clinical care. Neuropsychology assessments will be performed either 6-monthly or yearly (according to age) and include detailed neurocognitive and comorbidity evaluations. The study will employ 4 trained full-time Paediatric Neuropsychology Research Assistants (RAs) located across the UK to carry out all neuropsychological assessment visits. A total of 300 participants will complete both clinical standard of care as well as neuropsychological assessment visits. A further sub-set of up to 100 participants will complete clinical standard of care visits only.

Recruitment will be stratified by age and patients will be followed-up over a period of 3 years (recruitment will be phased out over 4 years):

- 30 patients per year age 0 to 2 years old (n = 80)
- 20 patients per year age 3 to 6 years old (n = 120)
- 10 patients per year age 7 to 16 years old (n = 140)
- 60 adult patients.

9) Alternative sources of data

Will alternative sources of data, other than the BPNSU, be used for case ascertainment (e.g. laboratory data, hospital activity analyses etc)?

Yes X **No ☐**

If yes, please describe:

a) the sources you intend to use (add any statements of support as appropriate)
b) the purpose of this additional source
c) how data will be collected and then matched between sources
d) the proposed analysis you intend to conduct

Participants will be identified by qualified research staff. This may be done from current lists of potential patients at clinics or using databases. Identification may involve a disease register, computerised search or review of medical records. The identification of patients will primarily be done by the direct healthcare team, however external referrals are a possibility from any potential clinician/GP that have heard about the study (i.e. referral) and believes that he/she has a potentially eligible patient.
The study is also supported by the charity Dravet Syndrome UK who will develop communication content to be shared through their website which we anticipate will reach families of people with Dravet Syndrome as well as healthcare providers. A central email address and study team phone number will be provided for enquiries.

10) Questionnaire

- Has your questionnaire been piloted?

Yes ☑ **No ☐**

- Is a follow-up questionnaire planned?

Yes ☑ **No ☐**

If yes, please give details (including timing of follow-up).

All study questionnaires are reviewed and piloted among clinical study teams.

11) Funding arrangements

Please outline the funding arrangements for your study.
BPNSU Costs: If your project is accepted you will be charged £1200 for up to 2 years (even if a project is 1 year) of your study. An invoice will be raised and sent to you on acceptance.
Any extra years that may be added would be a further £600 per year..
Funding arrangements should not only cover the BPNSU fee costs but also administrative costs including research assistance/secretarial salaries/stationery/postage etc.

This is an investigator led study sponsored by NHS Greater Glasgow and Clyde.
The study is funded via a combination of industry and charity grant funding.
The industry funders are Biocodex, Encoded Therapeutics Inc., Jazz/GW Pharmaceuticals, Stoke Therapeutics Inc. and UCB/Zognenix Inc.
Charity grant funding has been awarded by Dravet Syndrome UK and Dravet Syndrome Foundation.

The BPNA will send an invoice to you when your study is accepted onto the BPNSU website. Please provide the following information:

Purchase order number:	We would like to complete payment using credit card payment via our institution (University of Glasgow) purchasing officer, which I will arrange upon acceptance.
For the attention of:	
Full postal address: Postcode:	

12) Organisational arrangements

Please state the person responsible for the following:

- Person responsible for day-to-day administration (receiving reports, sending out questionnaires, correspondence with the BPSU): Dr Kirsty Hendry
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- Person responsible for scientific management of the study: Prof Andreas Brunklaus

- Person responsible for responding to clinical questions: Prof Andreas Brunklaus
- Person responsible for collating and analysing results: Prof Mark Kelson
- Additional academic or statistical support available: N/A

Please ensure that copies of all draft questionnaires and a signed letter of understanding are attached.

Signed: _____ ____
Date: 28/08/2023

(Principal investigator)

Name (in capitals): _PROFESSOR ANDREAS BRUNKLAUS____

Attached documents checklist:

BPNSU Letter of Understanding	**Yes ×**	**No ☐**
Questionnaire:	**Yes ×**	**No ☐**
Ethical Approval/Exemption:	**Yes ×**	**No ☐**
Copy of COREC application	**Yes ×**	**No ☐**
Study Protocol:	**Yes ×**	**No ☐**