ERGO No: 45724
IRAS No: 217804, 265580

PURA Syndrome Longitudinal Natural History Study. Research Protocol

STUDY TITLE

The PURA Global Network. Understanding PURA syndrome. PURA Syndrome Longitudinal Natural History Study. (A Musketeers' Memorandum Study).

PREFACE

This research protocol outlines the objectives, background, design and methods of the study. The protocol will be upheld and regulated by the study administrative team and clinical informatics team at the University of Southampton.

STUDY SUMMARY

Disease-causing variants in the PURA gene have recently been found to be a cause of neurodevelopmental delay in children and adults. People with PURA syndrome typically suffer from hypotonia (severe floppiness), feeding difficulties and breathing abnormalities in infancy. Most also have severe developmental delay and intellectual disability. Almost all remain non-verbal, and many develop seizures. Using a series of specifically designed questionnaires on a secure web-based interface we will collect clinical data about patients with disease-causing variants in the PURA gene internationally. Data will be collected from patients/guardians and clinicians.
A longitudinal study of the natural history of the condition is required for better understanding of the causes, range of manifestations, and progression of this rare disease.

RESEARCH OBJECTIVES

- To characterize the full spectrum of disease in PURA syndrome and the long-term prognosis, as this may assist in improved care for patients and development of treatment strategies for patients with PURA syndrome.
- To determine possible connections between disease-causing variants in PURA and the specific findings in the participant. This may help us predict what to expect and provide more tailored advice and care.
- To identify major quality of life issues and identify common care needs, in order to improve management of people with PURA syndrome and to guide future research to answer questions most relevant for people and families affected by the condition.
- To create a secure database of observational data to facilitate further research into PURA Syndrome.
- To promote further PURA- specific research involvement.

RESEARCH REFERENCE NUMBERS

IRAS Project ID:	217804 (England, Northern Ireland, Wales) 265580 (Scotland)
SPONSORS Details:	University of Southampton Research and Innovation Services Room 4079, Building 37, University of Southampton Highfield, Southampton SO17 1BJ Tel: +44 (0)23 8059 5058
FUNDERS DETAILS:	PURA Syndrome Foundation President (at time of submittal): Dominic Spadafore Contact: Dominic Spadafore, https://www.purasyndrome.org, for future updates of the Foundation Personnel c/o The University of Southampton, Faculty of Medicine Building 85, Life Sciences Building

Highfield Campus, Southampton SO171BJ
Email d.spadafore@pura-syndrome.org,

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: .....

Date: ...../...../.....

Name: (please print):

.....

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KEY STUDY CONTACTS

Chief Investigator	Professor Diana Baralle Professor Genomic Medicine, Consultant in Clinical Genetics, Southampton General Hospital, Tremona Road, Southampton SO16 6YD Work Email D.Baralle@soton.ac.uk Work Telephone 02381206162
System Administrator	CIRU - Clinical Informatics Research Team C/O National Blood and Transplant Service, MP 852, Coxford Road, Southampton, SO16 5AF, UK
Study Administrator	Dr Rebecca Mawby Clinical Research Fellow, Paediatric SPR Human Development and Health, University of Southampton, Southampton, Email: PURA@soton.ac.uk
Sponsor	University of Southampton Research and Innovation Services Room 4079, Building 37, University of Southampton Southampton, SO17 1BJ Tel: +44 (0)23 8059 5058
Funder(s)	PURA Syndrome Foundation President: Dominic Spadafore Contact: d.spadafore@pura-syndrome.org c/o The University of Southampton, Faculty of Medicine Building 85, Life Sciences Building Highfield Campus, Southampton, SO171BJ Telephone 02381206162 Fax 02381204346

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL SUPPORT GIVEN**
PURA Syndrome Foundation President: Dominic Spadafore c/o The University of Southampton, Faculty of Medicine Building 85, Life Sciences Building Highfield Campus, Southampton SO171BJ Telephone 02381206162 Fax 02381204346 Email d.spadafore@pura-syndrome.org	**£20,000**

ROLE OF STUDY SPONSOR AND FUNDER

The PURA Syndrome Foundation is funding the study. The Foundation is a global non-profit organisation. Their mission is to serve, educate and support research for families coping with the effects of PURA syndrome. The Foundation provides families with support and assistance, connecting them to a global community. This community offers support, educational resources and access to information about the latest medical research on PURA syndrome.

The PURA Syndrome Foundation, in collaboration with the University of Southampton is recruiting a clinical research fellow. The post-holder will initially undertake the position of study administrator and will complete phenotype analysis as part of this study. The fellow will help develop questionnaires, maintain the protocol and oversee the study system. This role is jointly funded by the PURA Syndrome Foundation and by an anonymous donor to the University of Southampton, UK.

The University of Southampton is sponsoring the study.

The PURA Syndrome Foundation and University of Southampton will work collaboratively on this study, as outlined in the Collaborative Research Agreement (RIS19164).

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Parents/guardians/relatives/personal consultees and clinicians are responsible for ensuring the accuracy of the data they provide. Global clinicians are responsible in confirming that their data entry conforms to their own Countries legal and ethical regulations.

The University of Southampton will act as sponsor for the study and will have data ownership.

The study administrative team will include the study administrator and research nurses. The study administrative team is based at the University of Southampton and all have been GCP (Good Clinical Practice) trained. At the initiation of the study the clinical research fellow will act as the study administrator and be responsible for establishing the study protocol, apply for ethical approval, create questionnaires and collate the research data. The study administrative team will be responsible for assessing patient and clinician eligibility, maintenance of the study, adding and overseeing records, and data exports. The Chief Investigator has overriding responsibility for the study design, ethical compliance, study conduct, outcome reporting and will act as custodian of the data.

The PURA Syndrome Foundation Study Advisory Steering Committee will be responsible for reviewing and approving requests from interested researchers wanting to access the data to conduct research on the dataset. The PURA Syndrome Foundation Board and Study Advisory Committee will be involved in the design, concept, and review of the protocol of the study and the study content. The PURA Syndrome Foundation Study Advisory Steering Committee includes: PURA Syndrome Foundation President, PURA Syndrome Foundation parent representative, assigned clinician, assigned researcher and Study Chief Investigator. The study CI will act as the sponsor representative.

The Clinical Informatics Research Unit (CIRU) is responsible for the development of the bespoke PURA database on the FormsVision BV ALEA software.

The PURA Syndrome Foundation and University of Southampton will work collaboratively on this study, as outlined in the Collaborative Research Agreement (RIS19164).

1 BACKGROUND

PURA syndrome is a rare genetic condition caused by disease-causing variants in the PURA gene. It was first described in the medical literature in 2014[1,2].

Disease-causing variants in the PURA gene have recently been found to be a cause of neurodevelopmental delay in children. PURA syndrome arises when one of an individual's two copies of the PURA gene does not function properly. It is almost always the result of a new (or de novo) genetic change. The PURA gene encodes a highly conserved protein known as Pur-alpha, with regulatory roles in DNA replication, gene transcription, RNA transport, and mRNA translation.

To date, all individuals with PURA syndrome have at least a moderate to severe degree of intellectual disability. Other typical features include: neurodevelopmental delay, hypotonia, feeding difficulties, breathing abnormalities, movement disorder and seizures. Other common manifestations include skeletal abnormalities, visual problems and endocrine dysfunction[3].

2 RATIONALE

This study will increase knowledge regarding the natural history of PURA syndrome by collating data about patient phenotype (such as developmental milestones, neurological history and health problems). The purpose of this research is to develop a deeper understanding of PURA syndrome. This is important as greater understanding of this condition will enable clinicians to make the diagnosis for more patients, and to provide more tailored future care and prognostic guidance for people with this rare disorder.

This research has the potential to highlight best practices for patient care, assist in the identification of research priorities and ascertain requirements for clinical trials and treatments. Long term, this information provides a better understanding of the necessary requirements, to develop dedicated clinics for PURA syndrome patients. Ultimately we hope that this will lead to better care for people with PURA syndrome in the future.

3 RESEARCH QUESTIONS/AIMS

- To characterize the full spectrum of disease in PURA syndrome and the long-term prognosis, as this may assist in improved care for patients and development of treatment strategies for patients with PURA syndrome.
- To determine possible connections between disease-causing variants in PURA and the specific findings in the participant. This may help us predict what to expect and provide more tailored advice and care.
- To identify major quality of life issues and identify common care needs, in order to improve management of people with PURA syndrome and to guide future research to answer questions most relevant for people and families affected by the condition.
- To create a secure database of observational data to facilitate further research into PURA Syndrome.
- To promote further PURA- specific research involvement.

4 STUDY PARTICIPANTS

Any child or adult with a genetic diagnosis of a pathogenic or likely pathogenic variant in the PURA gene, or a duplication or deletion of the PURA gene, will be eligible for inclusion.
Parents/guardians/relatives/personal consultees and clinicians will enter information about the study participant.

5 STUDY DESIGN

5.1 Framework

Patients will be included in the study if a pathogenic or likely pathogenic variant in the PURA gene, or a duplication or deletion of the PURA gene, has been located.

Using a series of specifically designed questionnaires, accessible via a secure web-based interface (ALEA software), the study will collect clinical data about patients internationally. This may also include uploading of radiological images, medical tests such as EEG, blood results and ECG results, and photographs. The questionnaires are systems based. The initial questionnaire subset will include questions regarding birth and neonatal history, genetic and family history, developmental milestones history, neurological history (including additional epilepsy subset if seizure history), endocrine history including puberty and growth history. All questionnaires will be reviewed and approved by the PURA Syndrome Study Advisory Steering Committee and PURA Syndrome Foundation board.

These will be continually developed and added, based on clinician and guardian reported associations and case studies. The aim would be that with time, there will be multiple questionnaires for different body systems.

To understand the natural history of the condition, the study participants' parent/guardian/relative/personal consultee/clinician will be asked to update the questionnaires annually. The questionnaires and clinical data collected will be paired with a pseudonymised patient ID, and stored in a separate server to the patient identifiable details.

The study will be publicised via the PURA Syndrome Foundation website, PURA Syndrome Foundation social media sites, PURA Syndrome conferences, other rare disease websites, other rare disease conferences and clinicians. Information regarding the study and how to participate will be available on the PURA Syndrome Foundation website.

The study participant's parent/guardian/relative/personal consultee can self-refer to the study by contacting the study administrator. Clinicians can be referred by the parent/guardian/relative/personal consultee or self-refer to the study by contacting the study administrator. Clinicians who self-refer will need to gain consent/personal consultee declaration from the parent/guardian/relative/personal consultee. Information leaflets and consent forms/personal consultee declaration forms will be available for clinicians to give to the the study participants' parent/guardian/relative/personal consultee.

After the study participants parent/guardian/relative/personal consultee/clinician have expressed interest in the study, an account will be generated. Access to the study questionnaires will only be allowed once consent/personal consultee declaration has been attained. Data will only be analysed and exported from patient IDs with a verified genetic diagnosis.

Contact details will be used to invite parents /guardians/relatives/personal consultees/clinicians to update information, access new questionnaires and update them on other research opportunities. They will be notified of on any changes in the study and when the study is to be decommissioned using these contact details.

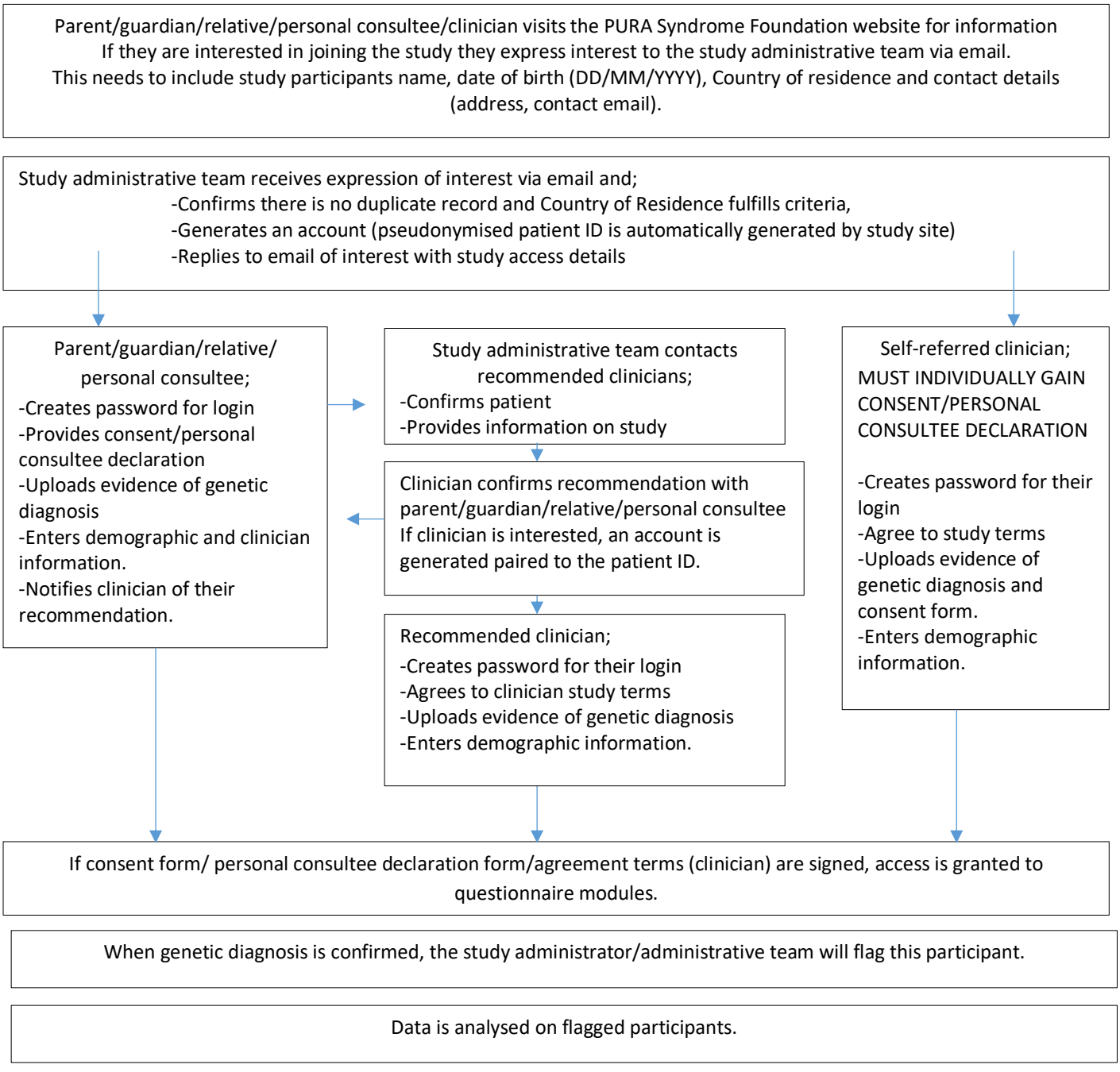
Pseudonymised results will be published on the PURA Syndrome Foundation website and presented at the annual PURA Syndrome Conference. Researchers can apply for pseudonymised data via the PURA Syndrome Foundation Study Advisory Steering Committee. Researchers will not receive the patients name, date of birth, address or contact details.

There is no study end-date or outcome data end-date. The continuation of the study will be considered annually by the PURA Syndrome Foundation Study Advisory Steering Committee and be guided by GDPR

data minimalisaton and storage limitation principles. Study decommissioning and retention of data after this point will follow the study protocol as guided by GDPR and GCP guidelines.

This research proposal has been very much driven by input and enthusiasm from the PURA Syndrome Foundation, as many families would greatly benefit from better understanding of this recently described condition and are very motivated and keen to be part of the process of learning more about it.

5.2 Study Flow Chart



5.3 Study Process

The study process for parents/guardians/relatives/personal consultees and recommended clinicians will be as follows:

1. Parent/guardian/relative/personal consultee wishing to understand or join the study can access online information on the PURA Syndrome Foundation public website. Those who wish to proceed, register 'an expression of interest' to the study administrative team via email (PURA@soton.ac.uk).
    a. They will need to email the study participants name, date of birth (DD/MM/YYYY), current Country of residence, and their contact details (address, contact email) to the study administrative team.
    b. Email trail will be deleted within 2 weeks of receipt.
2. Study administrative team creates an account using this information and the ALEA software allocates the study participant an account and pseudonymised patient ID.
    a. The name, date of birth, current Country of residence, and contact details are needed to generate an account, confirm there is no duplicate record and that the study participant meets inclusion criteria.
    b. It is likely the list of sanctioned Countries will change, if the participant was already involved in the study before sanctions were put in place, they can continue to be involved in the study. This list will be checked and updated annually and is the responsibility of the study administrative team.
3. The study administrative team will contact the parent/guardian/relative/personal consultee (via email) to make them aware an account has been generated.
    a. Recipients of the email will be informed of the web address to access the study, login will be the contact email address, requirement to set their own password and that minimal password requirements apply. This will be a generic email response with no identifiable information.
4. Parent /guardian/relative/personal consultee logs into account and is asked their language preference and to provide demographic information, clinician information, upload evidence of pathogenic PURA mutation/deletion/duplication, and complete either the online consent form or online personal consultee declaration form (for patients that are 16 years or older and live in England or Wales).
    a. The appropriate consent or personal consultee declaration form will be made available depending on the Country of residence and age of study participant.
    b. Contact details provided for clinicians needs to be the clinicians verifiable professional contact details.
    c. Access to the questionnaires will only be available after consent/personal consultee declaration form has been signed.
    d. All of the above information is patient identifiable and thus is stored separately to the clinical questionnaires.

e. Data will only be analysed on participants that have genetic diagnosis verified.
f. Parent/guardian/relative/personal consultee should notify clinicians of the recommendation, provide them with their pseudonymised ID and explain that the study administrative team will contact them.

5. Study administrative team will contact the recommended clinician via the contact details provided by the parent/guardian/relative/personal consultee. If the clinician expresses interest then a clinician account is created for the clinician.
    a. The clinician will be contacted from the PURA@soton.ac.uk email address, using the professional/institutional contact details that the study team has been provided with.
    b. When contacted, clinicians will be provided with information about the study (Information for Clinicians document) and the study participants name, date of birth and address.
    c. Clinicians should have been told that they have recommended by their patients' parent/guardian/relative/personal consultee (from the stored contact details or face-to-face). If they have not, they will need to contact the parent/guardian/relative/personal consultee (using their own contact details or face-to-face) to confirm recommendation. During this verification process, the parent/guardian/relative/personal consultee should provide the clinician with the pseudonymised ID.
    d. Clinician obtains appropriate ethical/institutional approval to partake in study.
    e. Clinician responds to study administrative team email account (PURA@soton.ac.uk); confirming the patient details and pseudonymised ID.
    f. An account is generated for clinician.
    g. The study administrative team will contact the clinician with the web address to access the study, login will be the contact email address, requirement to set their own password and that minimal password requirements apply. This will be a generic email response with no identifiable information.
    h. The clinician account will have their own login and will be linked with the recommending patient ID so they can view and enter information for that patient ID.
    i. In cases when clinicians have multiple patients they will have one login but can access and enter data for different patient ID's.
    j. For clinicians to access the questionnaires they must have agreed to the clinician study terms. This includes that they have appropriate national and institutional ethical and legal approval and they have confirmed recommendation/gained consent or personal consultee declaration.
6. Parent/guardian/relative/personal consultee/clinician provide online clinical data through a series of questionnaires.
7. Parent/guardian/relative/personal consultee/clinician will be sent email reminders annually asking them to update online clinical data and update contact details. They will also be emailed when new questionnaires are available on the system.

8. Participants are flagged when study administrative team confirm genetic diagnosis. Evidence of this must be from a genetic report, clinician letter or laboratory confirmation letter.
9. Pseudonymised research results and data will be collated by the study administrative team to provide information about the natural history and phenotype of PURA syndrome. Data will be collected at regular intervals with the planned first collection of information within a year of the study opening.
10. Pseudonymised research results and updates will be shared periodically via the PURA Syndrome Foundation public website as well as being published in peer reviewed scientific journals.
11. Researchers can apply for specified pseudonymised datasets, as outlined in the dissemination section.

The study process for self-referred clinicians will be as follows;

1. Clinicians wishing to understand or join the study can access online information on the PURA Syndrome Foundation public website. Those who wish to proceed, register 'an expression of interest' to the study administrative team via email (PURA@soton.ac.uk).
    a. Clinicians need to make contact using their professional/institutional contact details that can be verified.
    b. The clinician will need to email their patients name, date of birth (DD/MM/YYYY), address, current Country of residence, and their own professional contact details to the study administrative team.
    c. Email trail will be deleted within 2 weeks of receipt.
    d. The clinician must have gained consent/personal consultee declaration from their patient's parent/guardian/relative/personal consultee using the study clinic consent forms/personal consultee declaration forms and obtained appropriate ethical/institutional approval to partake in study.
2. Study administrative team creates a clinician account
    a. Patient name/date of birth/current Country of residence, and contact details are needed to generate an account, confirm they meet inclusion criteria, and there is no duplicate record.
    b. If a duplicate record exists, for example in the case where the patient has a record/patient ID but the clinician is not the recommended clinician, the clinician will be asked to contact the family and asks that they are added as a clinician to the patients details before an account is generated.
    c. If there is no patient account, a patient account will be generated with a patient ID, and the clinician account will be paired to that patient ID.
3. The study administrative team will contact the clinician with the web address to access the study, login will be the contact email address, requirement to set their own password and that minimal password requirements apply. This will be a generic email response with no identifiable information.
4. Clinician logs into account and is asked to provide demographic information, upload evidence of pathogenic PURA mutation/deletion/duplication, and agree to the study terms.

a. For clinicians to access the questionnaires they must have agreed to the clinician study terms. This includes that they have appropriate national and institutional ethical and legal approval and they have confirmed recommendation/gained consent or personal consultee declaration.
b. All of the above information is patient identifiable and thus is stored separately to the clinical questionnaires.

5. Clinician provides online clinical data through a series of questionnaires.
6. Clinician will be sent email reminders annually asking them to update online clinical data. They will also be emailed when new questionnaire modules are available on the system.
7. Pseudonymised research results and data will be collated by the study administrative team to provide information about the natural history and phenotype of PURA syndrome. Data will be collected at regular intervals with the planned first collection of information within a year of the study opening.
8. Pseudonymised research results and updates will be shared periodically via the PURA Syndrome Foundation public website as well as being published in peer reviewed scientific journals.
9. Researchers can apply for specified pseudonymised datasets, as outlined in the dissemination section.

5.4 Data Collection Schedule

Study enrollment will remain open throughout the period that the study remains active and can occur at any time frame after the diagnosis.

At time of enrollment; inclusion criteria, exclusion criteria and consent/personal consultee declaration will be confirmed. Once this is complete, parents/guardians/relatives/personal consultees will have access to the available questionnaires.

Annually the system will generate reminders to update clinical data. This will act as a new data set rather than override the existing data for that specific questionnaire module. The questionnaire data collected will remain in the server database and be added to rather than overwritten. This annual addition will allow us to map the natural history of the disease.

As more is understood about the condition, the questionnaire content may change or number of questionnaires increase to include other body systems. Participants will be contacted if there is a questionnaire added.

There will be no expiry of accounts in the case of inactivity.

5.5 Study Setting

This is an international study. Parents/guardians/relatives/personal consultees/clinicians internationally are eligible to access the web-based interface of this study and provide data.

Data will be entered online by both clinicians and parents/guardians/relatives/personal consultees.. The collection of patient information will be done via ALEA, a web-based data capture system supplied to CIRU (Clinical Informatics Research Unit) at the University of Southampton, by FormsVision BV.

Clinicians entering data into the study need to follow their own national ethical and legal regulations.

At the point of entry into the study the clinician will have entered institutional information and ensure all of these sites have access to the most current version of the protocol, consent and information forms.

Information and consent forms are available in English, French, Dutch, German, Danish, Portuguese, Spanish and Italian. As more patients are identified internationally, other languages will be translated as deemed appropriate. It is the submitting clinicians responsibility to ensure that the information and consent forms comply with national regulations. If adaptions and translations are required then the study administrative team will be available to aid in this.

5.6 Study Training

Members of the study administrative team will be involved in designing the specific PURA syndrome content held on the ALEA system and in designating access roles to users. The study administrative team will be trained by CIRU in orientating the ALEA system, data entry, and data export.

For those accessing the study, there will be information available on how to navigate the ALEA site.

5.7 Study Withdrawal

A parent/guardian/relative/personal consultee can withdraw the study participant at any time, without reason or repercussion. This can be requested by email or in writing to the study administrative team at PURA@soton.ac.uk or via the study withdrawal document on the study system. In keeping with GDPR guidelines, the study administrative team will acknowledge this request by email as soon as possible and within a month of receipt. In the event the request is made to the clinician, the clinician should inform the study administrative team or complete the study withdrawal document on the study system, as soon as possible. Once this has been received, the study administrative team will close the account to prevent uploading of any further information. If the study participant is withdrawn by their parent/guardian/relative/personal consultee and there is a corresponding clinician entry, neither the parent/guardian/relative/personal consultee or clinician will be able to add information to that study participants account. In these circumstances, the clinicians account will remain active so that they can still access other patients accounts, but they will no longer be able to access the “withdrawn” patients account. A clinician can withdraw from the study or unlink with patient’s accounts at any time. This can also be requested by email or in writing to study administrative team or via the study withdrawal document. In the event the clinician has multiple patients, they will need to communicate if they want to withdraw from the whole study or unlink with specific patient’s accounts. If they are doing this by the study withdrawal documents, this will need to be completed for each of the patients they wish to withdraw from. In the event the parent/guardian/relative/personal consultee wants to continue with the study but unlink from the clinician, they can request this by email or in writing to the study administrative team at PURA@soton.ac.uk or via the study withdrawal document on the study system.

Data that has been collected, exported or analysed prior to the closing of the account, will be available for analysis, research and publication. This is outlined in the Study Information Document and consent/personal consultee declaration form. After the closing of the account, data that has not been collected, exported or analysed will not be involved in further analysis or exported to researchers.

In keeping with GCP (Good Clinical Practice) quality standards for data entry to be audited, that data cannot be deleted and GDPR Article 17(3)(d) when the right to erasure is '*likely to render impossible or seriously impair the achievement of the [research] objectives*", the research will be exempt from the "right to erasure". That said, a parent/guardian/relative/personal consultee/clinician could overwrite their existing data with blanks at any point, which would effectively 'remove' the information from view by anyone that cannot view the audit trail and ensure that if data had not already been exported or analysed that it would not be included in future data exports.

5.8 Study Closure and Decommission

The study will remain open indefinitely. The continuation of the study will be considered annually by the PURA Syndrome Foundation Study Advisory Steering Committee. The continuation of the study will be subject to a successful outcome from regular applications to the University of Southampton ERGO committee and Research Ethics Committee (REC), the interval of this will be inline with the initial REC outcome.

When the PURA Syndrome Foundation Study Advisory Steering Committee decide to end the study they will instruct the current system administrator (CIRU) to decommission the study. Once CIRU has confirmed receipt for decommissioning they will request from FormsVision that all data from the production be left with the hosting provider (Interconnect BV). The length of time that data is stored after decommissioning, will be compliant with the current GCP regulations, at the time of decommissioning. At the time of decommissioning, the length that data is kept and whether this will then be erased, stored as part of a research database or in a secure repository will be decided by the PURA Syndrome Foundation Study Advisory Steering Committee, data custodian and the University of Southampton DPIA panel. This decision will be in keeping with up-to-date data laws and regulations. After decommissioning, the ongoing storage of this information by the hosting provider will be overseen and maintained by the data custodian. The data custodian will be required to update the University of Southampton DPIA panel on the storage of data information on a 24 monthly basis.

Data disposal will only occur in agreement with the Chief Investigator, data custodian, University of Southampton and PURA Syndrome Foundation Study Advisory Steering Committee.

6 SAMPLE AND RECRUITMENT

6.1 Patient Eligibility Criteria

Inclusion Criteria

Patients will be included in the study if a pathogenic or likely pathogenic PURA gene mutation has been located and reported. Patients with whole gene deletions or duplications of PURA will also be eligible for inclusion.

In circumstances where an individual with PURA Syndrome, PURA gene duplication or PURA gene deletion has died, the parent/guardian/relative/personal consultee can still access the study. The initial subset of questionnaires will be available with additional questions regarding cause and time of death. In these circumstances, parents/guardians/relatives/personal consultees will not receive annual reminders for study detail updates.

Exclusion Criteria

Any child or adult who is currently residing in a Country subject to UK sanctions or a Country on the USA State Sponsors of Terrorism list are excluded. The Countries currently excluded from the study are; Afghanistan, Belarus, Burma, Burundi, Central African Republic, Democratic Republic of Congo, Egypt, Eritrea, Republic of Guinea, Republic of Guinea-Bissau, Iran, Iraq, Lebanon, Syria, Libya, Mali, North Korea, Somalia, South Sudan, Sudan, The republic of Maldives, Tunisia, Ukraine, Venezuela, Yemen and Zimbawbwe. It is likely the list of sanctioned Countries will change, if the participant was already involved in the study before sanctions were put in place, they can continue to be involved in the study. This list will be checked and updated annually and is the responsibility of the study administrative team.

Due to the current legislation in Northern Ireland, we are unable to include patients that are 16 years or over from Northern Ireland. Patients from Northern Ireland recruited before 16 years of age will be able to be included up until their 16th birthday.

Data will only be analysed on patients who have a confirmed pathogenic mutation, duplication or deletion. Evidence of this must be from a genetic report, clinician letter or laboratory confirmation letter.

6.2 Clinician Eligibility Criteria

Clinicians can enter details about their patient, provided the patient they wish to enter data on fulfills inclusion criteria.

Clinicians who have self-referred to the study will need to get consent or personal consultee declaration (for patients 16 years and over residing in England and Wales). Hard copies of these forms will be available for this purpose. These will mirror the online consent/personal consultee forms with regards to clauses and translation. If during the course of the study the patient turns 16 years, then consent or personal consultee declaration for patients 16 years and over residing in England and Wales) will need to be re-attained using

the appropriate consent or personal consultee forms.
All clinicians will need to agree to the terms set out on the Clinician Study Terms document. This includes obtaining appropriate national ethical and institutional approvals. The clinician will need to complete the Clinicians Study Terms document at time of entry into the study, and will not be able to access the questionnaires if this is not completed.

6.3 Sampling

Gender: Male and female participants

Lower age limit: 0 Years

Upper age limit: 100 Years

The current number of globally diagnosed patients is approximately 270. There is no upper limit number for study participants. The aim is to recruit as many of these patients and their clinicians as possible. Given that this will mainly be by self-referral, international recruitment and in the context of it being a rare disease, sample size estimation cannot be computed.

6.4 Recruitment

We aim to offer every patient who fulfills inclusion criteria the opportunity to participate in this study. As this is a rare syndrome, the number eligible for the study is low, however as more is known about the condition and more patients identified, the participation rate is likely to increase.

To maximize recruitment, the study will be publicised via the PURA Syndrome Foundation website, PURA Syndrome Foundation social media sites, PURA Syndrome conferences, other rare disease websites, other rare disease conferences and patients clinicians. Further information regarding the study will be available on the PURA Syndrome Foundation website.

The aim is to enroll participants as soon after diagnosis as possible to follow the natural history of the disease. That said the age of diagnosis is variable and participants can choose to enter the study at any time point after their diagnosis.

The Foundation have been very active in the promotion of the study and have agreed to continue with this on their public website and at the global conferences they organize.

To maximize international recruitment, the information will be available in several languages including English, Spanish, French, Dutch, Italian, German, Portuguese and Danish.

7 ETHICAL AND REGULATORY CONSIDERATIONS

7.1 Consent

Informed consent from a parent/guardian/legal representative/nearest relative or a signed personal consultee declaration form is required for involvement in the study.

The study will require consent/personal consultee declaration for involvement in the study, with additional opt-in/ opt-out clauses for the uploading of photographs, dissemination to the PURA Syndrome Foundation (outside the European Economic Area), and dissemination to researchers outside of the European Economic Area (EEA). This is explained in the Study Information Document. If the parent/guardian/relative/personal consultee "opted in" for transfer of data to the PURA Syndrome Foundation Board, the Foundation will receive the study participants name and date of birth, address, and their contact email. This information will be used in the context of updating them about events, news and research opportunities by the PURA Syndrome Foundation.

The lawful basis for processing sensitive personal data is that it is 'necessary for archiving purposes in the public interest or scientific and historical research or statistical purposes.' The specific processing, handling or scientific research dissemination of the data is not specifically consented for, however this is clearly explained in the study information document and consent form/personal consultee declaration form.

The issue of valid consent needs to be carefully considered. The ability to provide consent depends on the capacity and thus cognitive ability of the individual. All of the patients identified to date have moderate-severe intellectual disability and the majority are children. Even if the diagnosis were made later it is unlikely that they would ever have capacity to consent. This research requires the participation of this patient cohort and cannot be carried out on an alternative population.

Consent for children (under 16 years of age) will need to be given by one of the parents or the main legal guardian. The definition of the main guardian/custodian, may change culturally and should follow national definitions, regulations and legislation. If the study participant is an adult (16 years or over) and they live in England or Wales, we will ask their personal consultee to provide an opinion for study involvement based on what they know of the study participants wishes and feelings, and to consider their interests. A personal consultee is defined as someone who cares for the study participant and is interested in the study participants welfare other than in a professional capacity. If the study participant is an adult (16 years or over) and lives in any Country with exception to England or Wales, we will ask that consent is attained from their legal representative such as a welfare attorney or welfare guardian. If they do not have a legal representative appointed then consent should be given by their nearest relative (as defined by the Mental Health (Scotland) Act 1984 relationship hierarchy).

The hierarchy of relatives in the Mental Health (Scotland) Act 1984, is as follows;

1. Spouse
2. Child
3. Father or mother
4. Brother or sister
5. Grandparent
6. Grandchild
7. Uncle or aunt
8. Nephew or niece

If the study participant was initially consented as a child, the appropriate consent/personal consultee declaration (as detailed above) will need to be completed once they become 16 years of age. This will be either generated by the study system if online consent was given or by the clinician if they initially took consent.

As more is learnt about the disease, the phenotype may theoretically broaden and include patients with less severe intellectual disability. If this becomes apparent, specific assent or consent forms will be designed so that patients have the opportunity to provide informed consent or be given the opportunity to withdraw from the study.

Prior to giving consent/personal consultee declaration, the parent/guardian/relative/personal consultee or clinician should have read the respective Study Information Document or Information for Clinicians document and have the opportunity to contact the study administrative team with any questions. There is no time deadline that this decision needs to be made by.

The online information sheets and consent forms will be available in multiple languages including English, Spanish, French, Dutch, Italian, German, Portuguese and Danish. When the appropriate language is not provided and if appropriate, use of an interpreter and arrangement for translation of letters and documents will be requested. English is likely to be the main language spoken by the majority of the study participants and their parents/guardians/relative/personal consultees/clinicians.

All of those persons providing consent/personal consultee declaration will be made aware that entering the study is voluntary and can be withdrawn at any time. Importantly they should also be reassured that it will not affect their clinician relationship if they choose not to enter the study.

Parents/guardians/relatives/personal consultees who are self-referring can access the consent/personal consultee declaration forms online. If they agree to the study terms, this constitutes an electronic signature, and therefore a waiver of documentation of informed consent is not required. The consent/ personal consultee declaration form will be saved, but there will be no hard copy with an ink signature. Given the

nature of the forms being online, a verbal conversation with the study team and individual consenting/giving a personal consultee opinion is not compulsory. In circumstances where there is confusion about the consent/personal consultee declaration or the parent/guardian/relative/personal consultee would like to discuss the study further, there will be information available online and study team contacts available.

“Self-referring” clinicians will need to get consent/personal consultee declaration using the hard clinic copies. If the patient is under 16 years of age, they will need to gain consent from one of the parents or the main legal guardian. If the patient is 16 years of age or older and lives in England or Wales, the clinician will need to get a personal consultee to sign the personal consultee declaration form. If the patient is 16 years or older and reside in any Country with the exception of England or Wales, they will need to get consent from the patients legal representative such as a welfare attorney or welfare guardian. If the patient does not have one appointed then they should get consent from their nearest relative, as defined by the Mental Health (Scotland) Act 1984 relationship hierarchy. If the study participant was initially consented as a child, the appropriate consent/personal consultee declaration (as detailed above) will need to be repeated once they become 16 years of age. Prior to accessing the questionnaires clinicians will need to confirm that they have gained consent/ personal consultee declaration in the clinician study terms document..

The parent/guardian/relative/personal consultee may feel under pressure to participate in the study if informed of it by the clinician who has made the diagnosis and has ongoing involvement in their childs/relatives/wards/persons care. This is a common situation in the genetics clinic, especially with regard to rare conditions. However, clinicians should not pressure involvement in the study and should clearly reassure parents/guardians/relatives/personal consultees that it is a choice to enter the study and that if they decline this will not affect ongoing care. Parents/guardians/relatives/personal consultees should be given ample time to read the study documents and ask questions.

The use of medical photography will need specific opt-in consent/personal consultee declaration; this is present as an additional opt-in tick-box on the online and clinic consent/ personal consultee declaration forms. Clinicians should not upload photographs without this. Clinicians will have access to the online consent/ personal consultee declaration form to view if this was given. In the event that photographs will form a research study, explicit consent/personal consultee declaration for publication will be required.

Parents/guardians/relatives/personal consultees/clinicians will be able to review their online consent/personal consultee declaration forms by accessing the ALEA system. Consent/ personal consultee declaration forms will be stored on the server in keeping with GCP protocol.

7.2 Confidentiality and Privacy

All participant details will remain confidential and participants' anonymity maintained in compliance with the General Data Protection Regulation (2016/679), Data Protection Act 2018 and the University of Southampton data management policy.

The data will be pseudonymised. Only the study administrative team, chief investigator and study participants parent/guardian/relative/personal consultee/clinician will have access to the linked information. The process of pseudonymisation will be randomly generated by ALEA and will not be generated from patient information such as age, initials or date of birth. Researchers will only receive exported datasets, with no direct identifiers.

It is a possibility given the small cohort of patients, that it may be possible to identify study participants indirectly from relatively basic demographic data such as age and ethnic origin or genetic mutation. This represents a challenge in rare disease research where there is only a small pool of patients eligible for recruitment. If possible, it is likely that identification will only be possible by those who already know the patient, such as clinicians, family members and other families in the PURA Syndrome community. This is explained in the Study Information Document and consent form/personal consultee declaration form.

When data is being requested for research, the PURA Syndrome Foundation Study Advisory Steering Committee will consider the dataset requested. The PURA Syndrome Foundation Study Advisory Steering Committee will not be provided with raw data but may ask the study administrative team for the number of patients in that data set cohort to aid with these decisions. The aim would be to keep data as anonymous as possible and be cautious in exporting data that could indirectly identify the individual. This is explained in the Study Information Document and consent form/personal consultee declaration form. Prior to publication, recipients of the datasets will be asked to provide a manuscript, which will allow another opportunity for the PURA Syndrome Foundation Study Advisory Steering Committee to minimise this.

Parents/guardians/relatives/personal consultees answering questions about medical history could be considered a breach of privacy. This needs to be balanced against the potential benefits of having a better understanding of PURA Syndrome and can only be conducted in these patients. Pseudonymisation will be key in minimising the effects of this.

7.3 Approvals

This is an international study. Prior to participants accessing the study, approval will have sought HRA approval including UK Research Ethics Committee approval (IRAS No: 217804 & 265580). It will also have had a data protection impact assessment (DPIA) and University of Southampton approval (ERGO 457241). Application has been approved for involvement in the Musketeers Memorandum (MM). The memorandum is a national agreement for rare-diseases studies, which allows a lead regional genetics centre to effectively review the project for all the other regional genetic R&D teams negating the need for individual negotiation.

In this case the lead R&D would be the University Hospital Southampton NHS Foundation Trust R&D department. This approval allows clinicians based at a regional genetics centres in the United Kingdom to enter data.

International ethical regulations are variable. Participating clinicians will need to follow their own institutional and National ethical regulations relating to consent and data management. This is in addition to the stipulations outlined in the study protocol and clinician study terms document. This is explained in the Information for Clinicians document.

The study administrative team will aim to help in the attainment of international ethical approval but cannot be responsible for applying for each application process. The protocol, sample forms and UK ethical proposals will be made available to aid in this. Ultimately the clinician submitting the information needs to take responsibility in confirming that the appropriate ethical approval has been granted.

7.4 Risk/Benefit Mitigation

There are no immediate or direct benefits to the study participants. However, the intended benefit is that by improving our understanding of this condition, we will enable clinicians to make the diagnosis for more patients, and to provide more tailored future care and prognostic guidance for people with this rare disorder. Participants will not receive any reimbursement, stipends or payments.

There is no experimental intervention or risk of physical harm. There is no financial cost to participants.

The main considerations of risk would be breach of confidentiality. This is minimized by pseudonymisation, defined access and enhanced database security. The data security measures are outlined in section 8.2, and are in place to minimize this. The protocol has been designed following GDPR, DPA and GCP guidelines/regulations.

The possibility of patient identification is discussed in section 7.2, and explained in the Study Information Document and consent form/personal consultee declaration form.

7.5 Right to rectification and Right to Erasure

In most cases, the parents/guardians/relatives/personal consultees will enter their own data so can control and rectify what is written. An audit trail will be incorporated into the questionnaires whereby any changes to the data originally entered will be documented. A table of all changes including the original value, new value, field, relevant visit details, who made the changes and why the changes were made, will be stored in a table in the study database.

If the parent/guardian/relative/personal consultee believes that data entered by the clinician is incorrect they should discuss this directly with their clinician. In the event that this is not resolved, the account will be ‘held’ preventing data export until this has been resolved.

In keeping with GCP (Good Clinical Practice) quality standards which requires data entry to be audited and GDPR Article 17(3)(d) when the right to erasure is '*likely to render impossible or seriously impair the achievement of the [research] objectives*", the research will be exempt from the "right to erasure". That said, a parent/guardian/relative/personal consultee/clinician could overwrite their existing data with blanks at any point, which would effectively 'remove' the information from view by anyone that cannot view the audit trail and ensure that if data had not already been exported or analysed that it would not be included in future data exports. An audit trail will be incorporated into the questionnaires whereby any changes to the data originally entered will be documented. A table of all changes including the original value, new value, field, relevant visit details, who made the changes and why the changes were made, will be stored in a table in the study database.

Parents/guardians/relatives/personal consultees/clinicians that have questions about data or want to make a data protection right request, can contact the study administrative team or chief investigator at the University of Southampton. If they have further concerns regarding this or wish to exercise these rights, they can access the University of Southampton data protection webpage request form at www.southampton.ac.uk/about/governance/subject-access-request-form.page, contact the University's Data protection officer at data.protection@soton.ac.uk or lodge a complaint with the information commissioners office at Wycliffe House, Water Lane, Wilmslow, SK9 5AF https://ico.org.uk/ The University registration number with this office is Z6801020. This information is available in the study information document and Information for Clinicians documents.

7.6 Indemnity

The sponsoring institution (University of Southampton) is required to provide insurance coverage and indemnity for the course of the study.

8 DATA MANAGEMENT AND GOVERNANCE

8.1 Data quality and accuracy

Parents/guardians/relatives/personal consultees and clinicians are responsible for ensuring the accuracy of the data they provide. We will ask that the questionnaires are answered as completely as possible and are not speculative. In most questions there is an option to answer do not know/unsure/not applicable to prevent speculative entries.

It is expected that parents/guardians/relatives/personal consultees/clinicians will update their data appropriately and accurately and there would be no benefit in entering incorrect or misleading information.

Researchers applying for data access should be aware of the methodology and make interpretations and recommendations with this in mind. The study administrative team will take all reasonable steps to generate and export high-quality data, the study administrative team, CI or University of Southampton will not be liable for the data content entered.

Quality of the data entered into the questionnaire data fields will be controlled by limited data entry, drop down options and predefined data formats. Range checks for chosen fields will automatically appear where data points are outside of a pre-specified range. Verification and explanation for the data point will be required and will subsequently appear in the query log for the study administrative team to check. Parents/guardians/relatives/personal consultees/clinicians will be asked not to include any identifiable information in these data fields.

Prior to the questionnaires being launched, they will be reviewed by parent/family members of the PURA Syndrome Foundation. After the initial questionnaire launch and at regular intervals, a random subset of data entries will be reviewed by the study administrative team. This will allow identification of unanswered questions, parental/guardian/relative/personal consultee/clinician feedback, and patient-clinician discrepancies. If this seems to be a regular occurrence with certain questions, then careful consideration will be made as to whether questions need amendment or whether the question needs to be removed from further data analysis. As parents/guardians/relatives/personal consultees/clinicians will enter data, the study administrative team will be guided by their feedback regarding difficult/confusing questions. Every opportunity will be given for feedback to be provided including on the study site, at the annual PURA Syndrome Foundation conference, via the Foundation or direct contact to the study administrative team.

Prior to export for external research data analysis, entries will be manually reviewed to ensure that there is no directly identifiable information exported.

8.2 Data flow and Data protection

All patient details will remain confidential and patients anonymity maintained in compliance with the General Data Protection Regulation (2016/679), Data protection Act (2018) and the University of Southampton data management policy.

When a patient account is generated for parent/guardian/relative/personal consultee data entry, it is assigned a unique pseudonymised patient ID by the ALEA software. When a clinician account is generated, their account is considered a ‘site’ and they can access and enter information for their specific patients. Medical and clinical records will only be identified via the patient ID with all other direct identifiers removed. Patient identifiable information will be stored in the server separately.

The collection of patient information will be performed using ALEA, an innovative web-based electronic data capture system created by FormsVision BV. FormsVision BV supplies the ALEA eCRF system to CIRU (Clinical Informatics Research Unit) at the University of Southampton. ALEA is widely used in clinical

trials internationally. CIRU will build a bespoke PURA database on the ALEA system. This PURA specific content will be created and designed collaboratively between the study administrator, CI and PURA Syndrome Foundation. This will be held on the CIRU production environment at https://prod.tenalea.net/ciru/DM/.

Forms Vision BV hires server space from InterConnect BV for hosting the ALEA study data. This is physically located in Den Bosch, the Netherlands. FormsVision BV can authorise any member of their staff to access the data centre. In these cases, staff receive a personal access card, which needs to be visible along with a valid identification card. The data centre staff accompanies authorised staff to the sector where the ALEA data is situated. Visitors sign in and out on arrival and departure. InterConnect BV is ISO 9001 and 27001 certified.

FormsVisions' Quality Assurance includes formal disaster management procedures for management of issues related to the operational environment. Measurements include failover, local data recovery, and site recovery. Each physical server is equipped with RAID5 disk redundancy, redundant power supply and redundant network connectivity. The server facilities in Den Bosch include both hot standby and cold standby servers. Hot standby servers (DBSHV3 and DBSSQL2) allow for near-instant failover to a running server in case of physical server failure. In case of logical server failure, cold standby servers (DBSHV4, DBSHV5) provide local data recovery in case the site is operational. In case of site failure, the disaster recovery procedure provides transfer of all operational services to the hosting facilities in Amsterdam.

Study data will be entered and accessed remotely via a web browser. Data is encrypted in transit using an SSL certificate. The study administrative team will define access rights for each account.

An audit trail will be incorporated into the eCRFs whereby any changes to the data originally entered will be documented. A table of all changes including the original value, new value, field, relevant visit details, who made the changes and why the changes were made, will be stored in a table in the study database.

The study administrative team may distribute information about other PURA Syndrome research studies (that are separate from the PURA Syndrome Longitudinal Natural History Study), after approval from the PURA Syndrome Study Advisory Steering Committee, to the contact email addresses of the parents/guardians of those involved in the study. This will be solely for publicising other studies that this cohort of patients will be eligible for. The study administrative team will have no role in the recruitment, neither provide patient contact information to these external research projects.

In the event that these emails are sent, there will be clear transparency that this is separate from the PURA Syndrome Longitudinal Natural History Study and that parents/guardians/relatives/personal consulees/clinicians are not obligated to participate in this research. The aim of this will be for increasing publicity of other PURA Syndrome projects, the study administrative team will not be involved in specific recruitment, validation of these studies or provide any patient contact addresses to these researchers.

Data table

Data will be accessed in the following manner:

- The study administrative team can view the entire system. In certain circumstances, when the clinician is in agreement the study administrative team may fill out the clinician modules by using patient medical notes. This input of information would not be through the clinicians account but via the study administrative team members account with an obvious audit trail. The study administrative team may also edit parent/guardian/ relative/personal consultee/clinician questionnaires to remove identifiable information.
- Parents/guardians/relatives/personal consultees can view and edit the data that they have supplied. They can also view but not edit the data the clinician has entered about their study participant.
- Clinicians can view and edit the data they have provided for their own patient/s. They can also view but not edit the data their patients parents/guardians/relatives/personal consultees have entered. They will only have access to their own patients information.

	Registration	Consent	Patient Identifiable Information	Genetic Evidence	Patient Questionnaires	Clinician Questionnaires
Parent/ guardian/ relative/ personal consultee	Hidden	Read/ Write*	Read/Write	Read/Upload	Read/Write	Read
Clinician	Hidden	Read	Read	Read/Upload	Read	Read /Write
Study administrative team	Read/Write	Read	Read/Write	Read/Upload	Read/Write	Read /Write
CI	Read	Read	Read	Read	Read	Read

Registration is the process where users are added to the system. When a patient account is generated it is assigned a unique pseudonymised patient ID by the ALEA software. When a clinician account is generated, their account is considered a 'site' and they can access and enter information for their specific patients. At registration, the study administrative team allocate accounts a role which allows/restricts data access and viewing.

Consent applies to the online consent/personal consultee declaration form that needs to be signed before access is granted to the study questionnaires. This is not related to the consent/personal consultee declaration that clinicians need to get from patients in the circumstance when the clinician self-refers.

Patient identifiable Information includes any information that directly identifies the patient. This includes patient name, patient date of birth, patient Country of residence and birth, and clinician details. Patient identifiable information will be stored separately to the questionnaires, which are only identifiable by pseudonymised patient ID. Clinician account will also have personal identifiable information such as their name and institution.

Genetic Evidence is the uploaded evidence of pathogenic PURA mutation/deletion/duplication. The study administrative team may need to upload this information. On completion of successful verification, patients are 'flagged' so their data can be processed. This will be stored with the patient identifiable information.

Patient Questionnaires are the questionnaires that the parent/guardian/relative/personal consultee are asked to fill in. There should be no patient identifiable details on these and only be identified by the patient ID. This may include anonymised patient reports. Clinicians will be able to see this data but not edit it.

Clinician Questionnaires are the questionnaires that clinicians are asked to fill in. There should be no patient identifiable details on these and only be identified by the patient ID. This may include anonymised patient reports. Parents/guardians/relatives/personal consultees will be able to see this data but not edit it.

Responsible members of the University of Southampton, the data system staff (FormsVision) or individuals from regulatory authorities may be given access to monitor and uphold data management regulations. This is explained in the Study Information Document.

8.3 Dissemination Policy

If the parent/guardian/relative/personal consultee have provided specific opt-in consent/personal consultee declaration, the PURA Syndrome Foundation Board will receive the study participants name and date of birth, address, and their contact email. The PURA Syndrome Foundation will use this information in the context of updating parents/guardians/relatives/personal consultees about events, news and research opportunities.

This transfer will be limited to the aforementioned list and will not include any link to pseudonymised ID, genetic or medical history. The transfer of this information and the fact that it is outside the European Economic Area (EEA) is explained in the Study Information document.and consent/personal consultee declaration form. Data will be transferred to the PURA Syndrome Foundation, via the University of

Southampton drop-off facility (https://dropoff.soton.ac.uk) and will be encrypted for transfer. The Collaborative Research Agreement between the University of Southampton and PURA Syndrome Foundation (RIS19164) outlines that data is managed inline with General Data Protection Regulations (GDPR). In addition, the PURA Syndrome Foundation has a GDPR compliant data policy.

Research use

Non-commercial third party researchers who wish to apply for the exported dataset will need to submit the data sharing application form including a signed data sharing agreement to the PURA Syndrome Foundation Study Advisory Steering Committee. These documents will be available on the PURA Syndrome Foundation website or by contacting the PURA Syndrome Foundation Study Advisory Steering Committee chair. Application forms should be sent to the PURA Syndrome Foundation Study Advisory Steering Committee chair.

All researchers will require approval from the PURA Syndrome Foundation Study Advisory Steering Committee. The PURA Syndrome Foundation Study Advisory Steering Committee includes: PURA Syndrome Foundation President, PURA Syndrome Foundation parent representative, assigned clinician, assigned researcher and the study Chief Investigator. The study CI will act as the sponsor representative. Meetings will be called within three months of an application being received and will require two-thirds of committee members to be present. For applications to be approved a majority vote is required by the PURA Syndrome Foundation Study Advisory Steering Committee.

Clinicians who have entered data onto the study system, and would like further access for research, need to apply in the same way.

At time of application, researchers will be required to provide a completed data sharing application form including a signed data sharing agreement. If approved, datasets will be exported via the University of Southampton in-house drop-off facility (https://dropoff.soton.ac.uk), which encrypts information for transfer.

Data will only be shared if researchers and their professional institution, have agreed to the terms of the data sharing agreement. The data sharing agreement stipulates that use and handling of data is compliant with GDPR regulations, revised Caldicott principle, Data Protection Act 2018 and their equivalent national legislations. It outlines the terms pertaining to data use, data storage, data access, data distribution, data destruction, data acknowledgements, academic publications, intellectual property rights and liability. This data sharing agreement will exist between the University of Southampton and the researcher's/data recipients professional institution. Researchers from outside of the EEA will also be required to sign an additional data transfer agreement.

For data to be distributed to researchers outside the European Economic Area (EEA), specific opt-in consent/personal consultee declaration must be obtained from parents/guardians/relatives/personal consultees. If this has not been received, parties outside of the EEA will not be able to receive the data.

The data storage needs to be appropriate and proportional to the nature of the data received. The researcher/data recipient should take responsibility in overseeing access to that dataset and ensuring this is proportional to achieve the specified research purpose. Researchers should make no attempt to identify or contact the data subject. Researchers should make no attempt to link data sets, unless approved by the PURA Syndrome Foundation Study Advisory Steering Committee. On completion of the purpose, the researcher/data recipient should delete or return the data, unless the PURA Syndrome Study Advisory Steering Committee has approved the continued storage of data at the researchers/data recipient's premises. When the project is completed and data deleted, the researcher/data recipient should confirm this in writing to the PURA Syndrome Study Advisory Steering Committee. These projects will subsequently be listed as complete on the publicly accessible research list.

Researchers who are requesting regular data exports will need to specify how often they would like data exports in their data application. Prior to receiving this export they should liaise with the study administrative team to clarify this is still required. Researchers that receive regular exports will be required to submit a brief report to the PURA Syndrome Foundation Study Advisory Steering Committee regarding their use of the data and justify their ongoing need for that data.

Researchers should be aware that a copy of the exported dataset will be maintained by University of Southampton Pure facility and each dataset will be provided with a data access statement and digital object identifier (DOI). Pure is the University of Southampton research information system. For the purpose of this study, Pure will allow a safe storage solution for the data exports, tracking of study output and will be linked with a DOI for researchers to link the dataset to their publication. Each dataset record will be held for a minimum of 10 years and have a data access statement with a DOI that researchers can cite in publication. If the researchers/data recipients publication, national or institutional guidelines require that it is held for longer than this, they will need to contact the study administrative team to discuss the length of time this is kept on Pure. Pure will hold a PURA study project, which will be associated with each exported dataset. Each dataset will be stored on Pure with "confidential visibility', which essentially means they are closed files and are only accessible to the dataset authors and specific University of Southampton members who have an appropriate and proportionate administration and security role. This may include the University library research engagement, research innovation services and isolutions team. The study administrative team will be responsible in requesting the exported dataset is added to Pure, requesting that this is restricted to "confidential visibility", and that there is an assigned DOI. Pure workshops are regularly organized to teach members of staff in the correct use of Pure. The process of how to deposit the file into Pure can be found at http://library.soton.ac.uk/ld.php?content_id=29296860.

The data access statement and DOI will be provided with the export to the researchers. The data access statement will be as follows; To comply with the University of Southampton's legal and ethical obligations, application to the PURA Syndrome Study Advisory Steering Committee must be obtained to get access to data in pseudonymised form derived from the raw study dataset. The study dataset for access is stored at the University of Southampton Pure repository, at [DOI address].

A list of the researchers using the data and their projects will be compiled by PURA Syndrome Foundation Study Advisory Steering Committee. This will be available on the PURA Syndrome Foundation website. Researchers will be responsible in updating the committee when they have completed the project to allow this list to be updated.

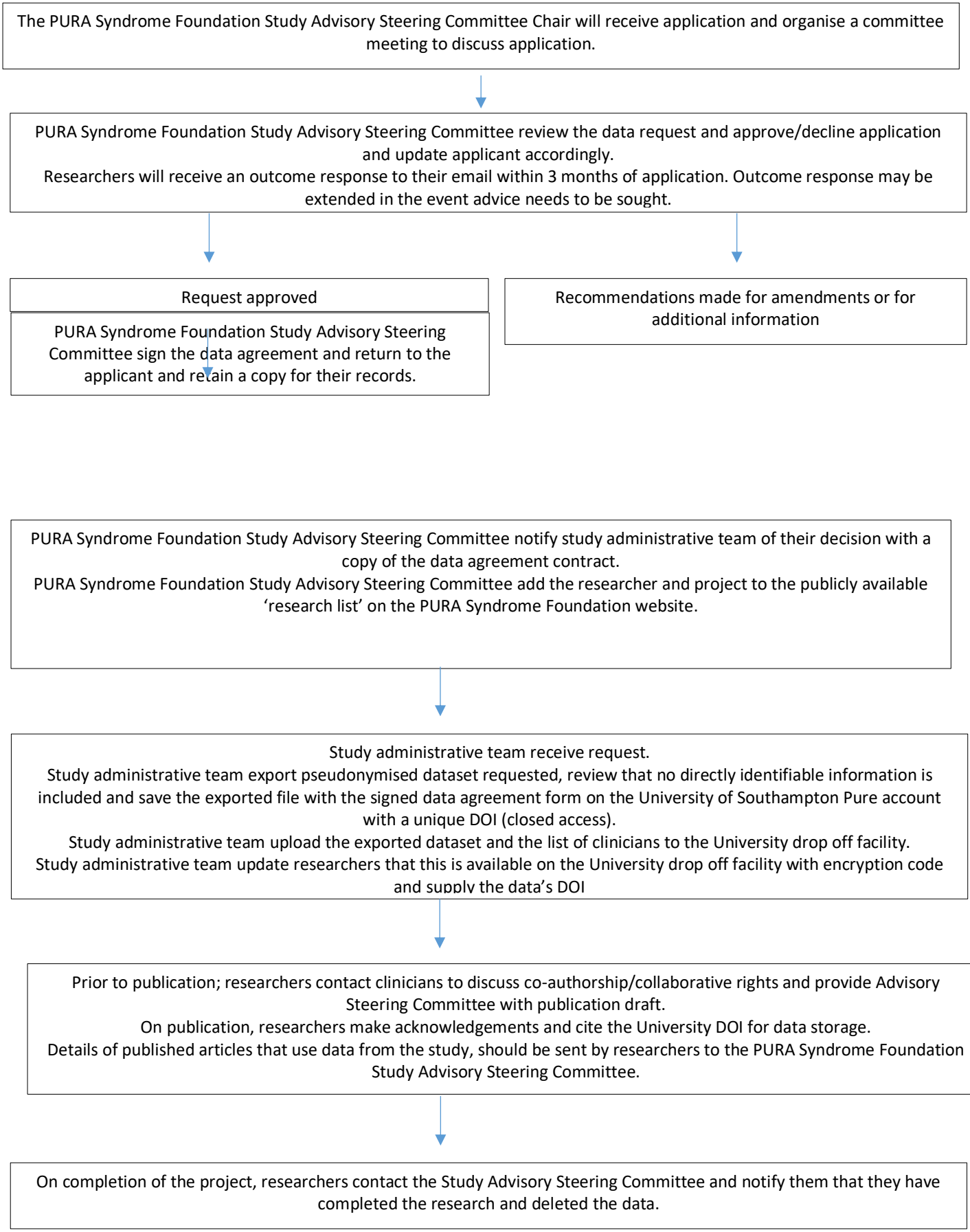
Pseudonymised research will also be collated by the study administrative team and shared via the PURA Syndrome Foundation public website and PURA Syndrome Foundation global conferences, as well as being published in peer reviewed scientific journals. This may include uploading disease-causing variants onto clinical databases such as Decipher or HGMDPro, in order to help clinicians make the diagnosis for future patients who may have similar variants.

The researcher/data recipient should submit a draft of any publication, publicity or other disclosure of results 30 days in advance to the PURA Syndrome Foundation Study Advisory Steering Committee, for review by the chief investigator (on behalf of the data provider/University of Southampton) and representatives of the PURA Syndrome Foundation Study Advisory Steering Committee.

Prior to publication, the researcher should review the risk of patient identification, and make every effort to minimise this risk.

Researchers should send published articles, to the PURA Syndrome Foundation Study Advisory Steering Committee so that they can share this with the PURA Syndrome community.

8.4 Data Request Pathway



8.5 Authorship and Acknowledgments

Authorship for publications made from data collected by the study should be guided by the most up to date International Committee of Medical Journal Editors (ICMJE) guidelines. All publications should acknowledge the study 'this publication was conducted from data collected in the PURA Syndrome Longitudinal Natural History Study. Funded by the PURA Syndrome Foundation, facilitated by the Clinical Informatics Research Unit (CIRU) at the University of Southampton, and sponsored by the University of Southampton. The study uses data entered by clinicians and families of individuals with PURA syndrome.' Researchers will receive a list of clinicians that have entered data into the dataset they are receiving and should make contact with these clinicians prior to publication to offer appropriate acknowledgment such as collaborator recognition or co-authorship. Researchers should make appropriate efforts to make this contact via the contact details provided, although in the absence of a response in an appropriate time frame, they can proceed in submission for publication. The study administrative team will hold a list of clinicians that have entered information and their institutions. Clinicians can opt-in or opt-out of having their contact details on this list.

Contact details received by researchers should be used for the purpose of collaborator and authorship rights. Researchers will not be provided with information that links the clinician to a particular patient record. Clinicians and researchers should not link information to try and identify patients from the study cohort or share information that makes it more likely that the patient will be identified. Sharing of additional information is not covered in the PURA Syndrome Natural History study consent/personal consultee declaration or study protocol. This will require independent consent that is transparent in this being autonomous to the study. The PURA Syndrome Natural History study will not be liable for information shared through these channels and the researchers will be in breach of the data sharing agreement.

Researchers and the research publisher should understand that the parents/guardians/relatives/personal consultees and clinicians provide the data. The study administrative team and PURA Syndrome Foundation will take all reasonable steps to protect the patient's privacy and anonymity. The study administrative team will take reasonable efforts to collect high quality data, however it makes no warranty and takes no liability about the data accuracy, or any responsibility or liability for the further analysis and interpretation of the dataset exported to researchers.

8.6 International Transfers

Data will be entered internationally. The study administrative team is based at the University of Southampton, UK and the data server in the Netherlands. Data handling will therefore be governed by GDPR and Data Protection Act, with both Countries located in the EEA (European Economic Area). The location of the server is explained in the Study Information Document and consent form/personal consultee declaration form.

Researchers internationally may apply for the pseudonymised exported dataset. They may be based outside of the EEA, where data transfer is not governed by the same regulations and would be regarded as a restricted transfer. To allow for this transfer, specific opt-in must be given by the parents/guardians/relatives/personal consultees during the consent/personal consultee declaration procedure. In addition, an agreement will exist between the University of Southampton (as the data controller) and researchers which specifies; compliance with GDPR and DPA for data management, further data use and acknowledgments.

8.7 Data governance checkpoints

Prior to data export the data will be reviewed to make sure there is no directly identifiable information included in the dataset such as name, geographical locations or date of birth.

At 6 monthly intervals, the study administrative team will randomly review a selection of questionnaires to identify any problem questions and will review feedback regarding difficult or confusing questions.

The PURA Syndrome Foundation Study Advisory Steering Committee will discuss applications for research data within three months of the application being made. The research list will be continually updated by the committee and reviewed formally on an annual basis.

The PURA Syndrome Foundation Study Advisory Steering Committee will annually convene to discuss and review; the current research projects and their proposed end dates, requests from researchers who are requiring sustained regular-interval data exports, study data output, study activity, ongoing running arrangements with CIRU/FormsVision/Interconnect, and continuation/decommissioning of the study. This will be used to provide an annual update to the data custodian, which will be needed to update the University DPIA panel.

At 2 yearly intervals the data custodian will meet with the University DPIA panel to provide a study update.

8.8 Data Format

The study web-interface is provided by FormsVision and customised for the purpose of this study by CIRU. FormsVision abides by CDISK and ODM formatting standards so the data can be moved and updated. The software is continually being updated inline with technological advancements enabling ongoing access to the data format. There will be standardized and consistent data export procedure, however the format can be specified allowing different researchers with different programmes to access the data. Data formats currently available are SAS, SPSS, Excess and Access.

8.9 Ownership

As the sponsor of the study, University of Southampton will have data ownership. The PURA Syndrome Foundation and University of Southampton will work collaboratively regarding data access, data use and ongoing maintenance of the study, as outlined in the Collaborative Research Agreement (RIS 19164) between these two parties.

Parents/guardians/relatives/personal consultees retain control of the data they provided according to the in-force regulations at the time data was given. This is for example with regards to lawful basis, withdrawal and right to rectification.

Professor Baralle will act as custodian of data on behalf of the PURA Syndrome Foundation and University of Southampton. In the event that Professor Baralle position changes, a new custodian will be allocated as agreed by Professor Baralle, University of Southampton and PURA Syndrome Foundation. FormsVision BV owns the ALEA software that CIRU will build the PURA database on. CIRU have a contract with FormsVision BV to build study databases onto the system, on behalf of the University of Southampton.

9 REFERENCES

1. Lalani SR, Zhang J, Schaaf CP, et al. Mutations in *PURA* Cause Profound Neonatal Hypotonia, Seizures, and Encephalopathy in 5q31.3 Microdeletion Syndrome. *American Journal of Human Genetics*. 2014;95(5):579-583. doi:10.1016/j.ajhg.2014.09.014.
2. Hunt D, Leventer RJ, Simons C*, et al.* Whole exome sequencing in family trios reveals *de novo* mutations in *PURA* as a cause of severe neurodevelopmental delay and learning disability. *Journal of Medical Genetics* Published Online First: 23 October 2014. doi: 10.1136/jmedgenet-2014-102798
3. Reijnders MRF, Janowski R, Alvi M, Self JE, van Essen TJ, Vreeburg M, et al. PURA syndrome: clinical delineation and genotype-phenotype study in 32 individuals with review of published literature. J Med Genet. 2018 Feb;55(2):104–13.

10 APPENDICES

1. Study Information Document V5 19.7.19
2. Information for Clinicians Document V3 22.07.19
3. Online Consent Document V4 25.6.19 (Children under 16 years)
4. Clinic Consent Document V4 25.6.19 (Children under 16 years)
5. Online Personal Consultee Declaration Form V1 27.6.19 (adults 16 years or older without capacity in England or Wales)
6. Clinic Personal Consultee Declaration Form V1 27.6.19 (adults 16 years or older without capacity in England or Wales)
7. Online Consent Document V1 26.6.19 (adults 16 years or older without capacity in all other Countries other than England or Wales)
8. Clinic Consent Document V1 26.6.19 (adults 16 years or older without capacity in all other Countries other than England or Wales)
9. Clinician Study Terms Document V4 19.7.19
10. Data Access Application and Data Sharing Agreement (combined document) V1
11. Patient Demographic Information Document V1 23.01.19
12. Clinician Demographic Information Document V1 10.1.19
13. Questionnaire: Q1 Patient Genetic and Family History V2 20.5.19
14. Questionnaire: Q1 Clinician Genetic and Family History
15. Questionnaire: Q2 Patient Pregnancy, Birth and Newborn V1 9.1.19
16. Questionnaire: Q2 Clinician Pregnancy, Birth and Newborn V1 12.1.19
17. Questionnaire: Q3 Patient Developmental History V1 14.1.19
18. Questionnaire: Q3 Clinician Developmental History V1 14.1.19
19. Questionnaire: Q4 Patient Neurological History V1 15.1.19
20. Questionnaire: Q4 Clinician Neurological History V1 15.1.19
21. Questionnaire: Q5 Patient Epilepsy/Seizure History V1 23.1.19
22. Questionnaire: Q5 Clinician Epilepsy/Seizure History V1 28.1.19
23. Questionnaire: Q6 Patient and Clinician Growth History V1 23.01.19
24. Questionnaire: Q7 Clinician Endocrine History V1 28.01.19
25. Questionnaire: Q7 Patient Endocrine History V1 23.01.19
26. Study Withdrawal Form (Clinician version) V1 10.1.19
27. Study Withdrawal Form (Patient version) V1 10.1.19
28. Cause of Death Information Document V1 15.01.19
29. CV PI Dr Diana Baralle
30. Collaborative Research Agreement between the University of Southampton and PURA Syndrome Foundation (RIS19164) V1
31. Confirmation email from Musketeers Memorandum