**SCREENING FOR FABRY DISEASE IN HAEMODIALYSIS POPULATION**

**SoFAH STUDY**

**PROTOCOL VERSION 1.0 (Feb 2021)**

**RESEARCH REFERENCE NUMBERS**

|  |  |
| --- | --- |
| **IRAS Number:** | The unique identifier generated by IRAS for the project. This will be the primary reference number used by REC, HRA and sites to identify the project and should be quoted in all project related correspondence. |
|  |  |
| **SPONSORS Number:** | Generated by the Sponsor. Enter if applicable |
| **FUNDERS Number:** | Generated by the funder. Enter if applicable |

# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor’s SOPs, and other regulatory requirements as amended.

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 clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly 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.

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| **For and on behalf of the Study Sponsor:** |
| Signature: ...................................................................................................... |  | Date: ....../....../...... |
| Name (please print):...................................................................................................... |  |  |
| Position: ...................................................................................................... |  |  |
| **Chief Investigator:** |
| Signature: ...................................................................................................... |  | Date: ....../....../...... |
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| Name: (please print):......................................................................................................  |  |  |
| Position: ......................................................................................................  |  |  |

**KEY TRIAL CONTACTS**

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| Joint-sponsor(s)/co-sponsor(s)  | Not applicable |
| Funder(s) | Sanofi- GenzymeAddress: 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford, OX4 2SU, UK.Tel No.: [01865 405200](https://www.google.co.uk/search?ei=hOMYW5S7Isz2gQbykLLgBQ&q=sanofi%20genzyme%20uk&oq=sanofi+genzyme&gs_l=psy-ab.3.1.0l10.64694.66837.0.68021.14.11.0.3.3.0.162.1126.6j5.11.0....0...1c.1.64.psy-ab..0.14.1150...35i39k1j0i67k1j0i131k1j0i131i67k1j0i20i263k1.0.bTTpepicIWM&npsic=0&rflfq=1&rlha=0&rllag=52462528,-954200,124656&tbm=lcl&rldimm=16796761844955137803&ved=0ahUKEwj0-MLOiMHbAhVEasAKHevgAjoQvS4IUzAH&rldoc=1&tbs=lrf:!2m1!1e3!3sIAE,lf:1,lf_ui:4) |
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**TRIAL SUMMARY**

|  |  |
| --- | --- |
| Study Title | Screening for Fabry Disease in Haemodialysis Population |
| Internal ref. no. (or short title) | SoFAH study |
| Clinical Phase  | *Not applicable* |
| Study Design | Epidemiology; Multi-centre; Cross-sectional study  |
| Study Participants | Patients receiving haemodialysis under the care of six renal units in the West Midlands |
| Planned Sample Size | 2,200 patients |
| Treatment duration | *Not applicable* |
| Follow up duration | *Not applicable* |
| Planned Study Period | 12 months |
|  | Objectives | Outcome Measures |
| Primary | * To examine the prevalence of Fabry disease in patients receiving haemodialysis in the U.K.
 | * Dried blood spot (DBS) α-gal-A enzyme assay, Lyso-GB3 assay and GLA genetic testing
 |
| Secondary | * To examine the false positive rate of DBS test for Fabry disease in haemodialysis population.
* To examine the phenotypical and genetic characteristics of any new cases of Fabry disease identified by the study.
* To compare the characteristics of previously undiagnosed Fabry disease cases to patients without Fabry disease amongst haemodialysis population.
* Cascade screening and three generation genetic testing of index patients
 | * Age
* Gender
* Ethnicity
* Cardiovascular history
* Previous renal diagnosis
* Other known co-morbidities (from clinical notes)
* Renal biopsy results where available
* α-gal-A enzyme results
* Lyso-GB3 assay
* Genetic mutational analysis results
 |

**FUNDING AND SUPPORT**

|  |  |
| --- | --- |
| **FUNDER(S)** | **FINANCIAL AND NON FINANCIAL SUPPORT GIVEN** |
| **Sanofi- Genzyme**Address: 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford, OX4 2SU, UK.Tel No.: [01865 405200](https://www.google.co.uk/search?ei=hOMYW5S7Isz2gQbykLLgBQ&q=sanofi%20genzyme%20uk&oq=sanofi+genzyme&gs_l=psy-ab.3.1.0l10.64694.66837.0.68021.14.11.0.3.3.0.162.1126.6j5.11.0....0...1c.1.64.psy-ab..0.14.1150...35i39k1j0i67k1j0i131k1j0i131i67k1j0i20i263k1.0.bTTpepicIWM&npsic=0&rflfq=1&rlha=0&rllag=52462528,-954200,124656&tbm=lcl&rldimm=16796761844955137803&ved=0ahUKEwj0-MLOiMHbAhVEasAKHevgAjoQvS4IUzAH&rldoc=1&tbs=lrf:!2m1!1e3!3sIAE,lf:1,lf_ui:4) | **Financial**  |

# ROLE OF STUDY SPONSOR AND FUNDER

The study is sponsored by University Hospital Birmingham NHS Foundation trust, which oversees the conduct of the study.

Sanofi-Genzyme provides financial support to the study.

# ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

SoFAH study will be coordinated by the study co-ordinator at the Research and Development department, University Hospitals Birmingham NHS foundation Trust, according to the current guidelines for Good Clinical Practice. Participating renal units may be monitored by trial manager to confirm compliance with the protocol and the protection of patients’ rights as detailed in the Declaration of Helsinki.

The chief investigator (CI) takes overall responsibility for the conduct of study. A principal investigator (PI) will be nominated at each renal unit and will take responsibility for all activity conducted at site. Any delegated or devolved responsibility will be documented on the delegation log. It is the PI’s responsibility to ensure that staffs are appropriately trained to perform the tasks that they are delegated to and that it is appropriately documented on the delegation log.

**Protocol contributors**

Prof Indranil Dasgupta designed the study. Dr Khai Ping Ng drafted the protocol.

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| --- | --- |
| **KEY WORDS:** | Fabry Disease, Haemodialysis, prevalence, undiagnosed, Midlands, UK. |

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**LIST OF ABBREVIATIONS** *(to be completed when protocol is finalised)*

Define all unusual or ‘technical’ terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE Adverse Event

AR Adverse Reaction

CA Competent Authority

CI Chief Investigator

CRF Case Report Form

CRO Contract Research Organisation

CTA Clinical Trial Authorisation

CTIMP Clinical Trial of Investigational Medicinal Product

DMC Data Monitoring Committee

EUCTD European Clinical Trials Directive

EudraCT European Clinical Trials Database

GCP Good Clinical Practice

GMP Good Manufacturing Practice

IB Investigator Brochure

ICF Informed Consent Form

ICH International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.

IDMC Independent Data Monitoring Committee

ISF Investigator Site File

ISRCTN International Standard Randomised Controlled Trials Number

NHS R&D National Health Service Research & Development

NIMP Non-Investigational Medicinal Product

PI Principal Investigator

PIC Participant Identification Centre

PIS Participant Information Sheet

QA Quality Assurance

QC Quality Control

REC Research Ethics Committee

SAE Serious Adverse Event

SAR Serious Adverse Reaction

SDV Source Data Verification

SOP Standard Operating Procedure

SmPC Summary of Product Characteristics

SSI Site Specific Information

SUSAR Suspected Unexpected Serious Adverse Reaction

TMG Trial Management Group

TSC Trial Steering Committee

TMF Trial Master File

# TRIAL FLOW CHART

Figure 1.0: Trial flow chart



Figure 2.0: SoFAH screening algorithm

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**STUDY PROTOCOL**

**SoFAH study: Screening for Fabry Disease in Haemodialysis Population**

# 1 BACKGROUND

Fabry disease is an X-linked inherited lysosomal storage disorder. A mutation of the GLA gene leads to the deficiency of a lysosomal hydrolase enzyme, α-galactosidase A. It results in progressive accumulation of glycophospholipids (predominantly globotriaosylceramide 3, Gb3) in cells throughout the body, resulting in multisystem disorder and premature death [[1-3](#_ENREF_1)]. Clinical manifestations include anhidrosis or hypohidrosis, acroparaesthesia, corneal opacities, angiokeratomas, sensorineural deafness, non-specific bowel disturbance, progressive proteinuric kidney disease, fibrotic cardiac disease, progressive hypertrophic cardiomyopathy and cerebrovascular disease [[2](#_ENREF_2)]. Though Fabry disease is an X-link disorder, both male and female can be affected. Patients may present in either classic form, which has severe clinical phenotype, or atypical variant, which presents later in the 3rd to 7th decade of life [[3](#_ENREF_3), [4](#_ENREF_4)]

The prevalence of Fabry disease was previously estimated to be 1 in 117,000 to 1 in 833,000 [[5](#_ENREF_5), [6](#_ENREF_6)]. However, recent large genetic screening programs of newborns reported incidence of 1 in 1,300 to 1 in 7,800 of Fabry disease in male [[7-10](#_ENREF_7)], demonstrating that Fabry disease is more frequent that previously expected.

A systematic review carried out nearly a decade ago estimated prevalence of Fabry Disease amongst end-stage kidney disease population to be 0.33% in men and 0.1% in women [11]. However, two large national screening studies in Europe, using blood spot test in end stage kidney disease patients on haemodialysis suggested the prevalence is much higher at around 3.5%. [15,16]. The diagnosis of Fabry Disease is frequently delayed; according to a registry study the average delay is 14 years in males and 19 years in females [7] [[11](#_ENREF_11)]. In the UK, screening is not routinely done but available in the forms of dried blood spots which measures the α-galactosidase A activity or detection of urine total globotriaosylceramide detection. Female carriers may have normal to low enzyme activity due to mosaic x-inactivation, therefore plasma level of Lyso-GB3 should be measure and genetic testing may be required.

# 2 RATIONALE

Due to its non-specific manifestations, Fabry disease especially the later-onset variant, is often

under-diagnosed. In addition, as mentioned above, there is often a significant delay in

diagnosis [[7](#_ENREF_3)]. Our experience in the University Hospitals Birmingham Fabry Disease Clinic

suggests that the disease is often diagnosed late in kidney patients. Screening of high-risk

groups is therefore important for case finding [[12](#_ENREF_12)]. Though a previous UK based screening of

155 male on haemodialysis did not identify any new cases of Fabry disease, it was limited by

its small sample size [[13](#_ENREF_13)]. The prevalence has been found to be higher in other populations

[15,16]. The aim of this study is to evaluate the prevalence of Fabry disease in a large UK

haemodialysis population, especially in those who are not known to have a diagnosis of their

primary kidney disease (chronic kidney disease of unknown aetiology). This may ultimately

change the investigation protocol for patients with chronic kidney disease especially those

with an unknown cause. This will also lead to cascade screening of relatives of identified

patients which in turn will facilitate early institution of enzyme replacement therapy.

Moreover, the identified patients in the haemodialysis population may benefit from enzyme

replacement therapy in terms of their cardiac involvement, i.e. coronary artery disease, cardiac failure and death [17].

## **2.1 Assessment and management of risk**

## There is no significant additional risk associated with the screening test as blood is sampled during haemodialysis.

## All male participants are screened using alfa-galactosidase enzyme and Lyso-GB3 assay. A high threshold of < 30% for alfa-galactosidase enzyme level and Lyso-GB3 level of > 2.7 nm are set to avoid false negative results. If either of the enzyme or Lyso GB3 level is abnormal, further genetic testing for GLA mutation will be performed in order to confirm the diagnosis of Fabry disease.

## Due to mosaic x-inactivation, all female participants will be screened using alfa-galactosidase enzyme level, lyso-GB3 assay as well as genetic mutation test in order to confirm diagnosis of Fabry disease.

There is a potential risk of psychological impact on patient who is diagnosed with Fabry disease through this study. This risk will be mitigated and managed by the support of University Hospitals Birmingham Fabry Disease specialist clinic.

# 3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

**3.1** **Primary objective**

To estimate the prevalence of Fabry Disease in a large haemodialysis population in the United Kingdom.

**3.2 Secondary objectives**

* + To examine the false positive rate of dried-blood spot alfa-galactosidase enzyme test for Fabry disease in male and female haemodialysis population.
	+ To examine the false positive rate of dried-blood spot lyso-GB3 test for Fabry disease in male and female haemodialysis population.
	+ To examine the phenotypical and genetic characteristics of any new cases of Fabry disease identified by the SoFAH study.
	+ To determine cost-effectiveness of screening for Fabry disease in haemodialysis population.

**3.3 Outcome measures**

**3.4 Primary endpoint/outcome**

* Prevalence of Fabry disease in haemodialysis population in the UK as defied by dried blood spot alfa-galactosidase A enzyme activity, Lyso-Gb3 level and genetic mutation of GLA analysis.

**3.5 Secondary endpoints/outcomes**

* Clinical characteristics of new cases of Fabry disease identified by the study, including age, gender, ethnicity, duration of onset, cardiovascular history, previous renal diagnosis and previous renal biopsy report.
* Fabry disease symptoms questionnaire results.
* EQ5D-5L questionnaire

**3.6 Exploratory endpoints/outcomes**

 None

# 4 STUDY DESIGN

 SoFAH is a cross-sectional, epidemiological screening study of Fabry disease.

# 5 STUDY SETTING

#  It is a multi-centre study, including all haemodialysis population under the care of six renal units in the Midlands, in the UK.

Six centres will be included in the study (data retrieved from the renal registry 2015) giving an estimated study population of 2808.

|  |  |
| --- | --- |
| **Sites** | **Number of patients on haemodialysis** |
| University Hospitals Birmingham  | 1427 |
| Royal Stoke University Hospital | 334 |
| University Hospital Coventry and Warwickshire | 354 |
| Dudley Russells Hall Hospital | 172 |
| Wolverhampton New Cross Hospital | 318 |
| Royal Shrewsbury Hospital | 203 |
| **Total** | **2808** |

# 6 ELIGIBILITY CRITERIA

**6.1 Inclusion criteria**

All patients receiving haemodialysis under the care of the six participating renal units:

* Age 18 years and above
* Capable of giving informed consent

**6.2 Exclusion criteria**

None

# 7 STUDY PROCEDURES

 Refer to Figure 1.0: Study Flow Chart and Figure 2.0: SoFAH Fabry Screening algorithm.

**7.1 Recruitment**

**7.1.1 Patient identification**

All adult patients receiving haemodialysis under the care of the six participating renal units are identified and recruited.

* Each renal unit provides the list of patients on haemodialysis.
* Research nurse provides all eligible patients with Patient Information Sheet on SoFAH study.
* Research nurse obtains informed, written consent from willing participants.

Anonymised screening log will be maintained at each site in order to monitor reasons for non-participation and ensure representativeness of recruited participants.

Data will be recorded in an electronic database which will be developed for the study.

**7.2 Consent**

All eligible patients are given SoFAH patient information sheet (PIS) and consent form by the research nurse during one of their haemodialysis sessions. All potential participants will be given sufficient time to consider their participation in the study and opportunity to ask questions regarding the study after receiving the PIS, following which the consent will be taken.

Written, informed consent is obtained by research nurse prior to the participant undergoing procedures that are specifically for the purposes of the study. In the case of participants who cannot read or write or require translators, the study will allow a witness to sign on a participant’s behalf (in the case of problems with reading or writing), allow a witness to date the form on behalf of the participant and allow hospital or personal interpreter.

The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

 The Principal Investigators (PI) retains overall responsibility for the informed consent of participants at their sites and ensures that the research nurses who are delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

**7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable**

All patients will be consented for Fabry disease genetic testing.

**7.6 Baseline data**

All consented participants’ demographic and clinical data will be collected, which include age, gender, ethnicity, clinical symptoms associated with Fabry disease, cardiovascular history, previous renal diagnosis, previous renal biopsy report and dialysis vintage.

**7.7 Screening of Fabry Disease**

* Whole venous blood samples (1 ml) will be sampled from all participants during haemodialysis from the dialysis line and apply to the dried blood spot card (see appendix 1).
* Dried blood spot specimens will be sent for analysis to the Archimed Laboratories, Europe.
* The dried blood spot results will be returned by the laboratories to the study coordinator and chief investigator.

**7.8 Long term follow-up assessments**

All participants who were tested negative for Fabry disease will be notified via letter by the research team and chief investigator. No further visits or follow-up will be required unless the participant’s Fabry test is positive.

The local kidney consultants (PI) involved in this study will inform the participants who are tested positive for Fabry disease of the new diagnosis. They will be referred to the specialist Fabry disease clinic at the Queen Elizabeth Hospital in Birmingham (QEHB) as part of their routine NHS care for further assessment, counselling and support. In addition, this will also lead to cascade screening of relatives of newly diagnosed participants by the specialist Fabry disease clinic, which in turn will facilitate early institution of enzyme replacement therapy.

**7.10 Withdrawal criteria**

 Participants will be withdrawn from the study if they choose not to continue with the study.

**7.11 Storage and analysis of samples**

All blood samples (dried blood spot) will be sent for analysis to the Archimed Laboratories, Europe. Samples will be disposed of 6 months after analysis by the Archimed Laboratories.

## **7.12 End of Study**

The study ends after all participants complete their Fabry disease screening tests, and that the results for the screening tests are valid and complete.

# 8 STATISTICS AND DATA ANALYSIS

**8.1 Sample size calculation**

All the adult haemodialysis patients, approximately 2,800 patients, under the care of the six renal units are invited to the study. We estimate that the response rate for patients agreeing to participate to be 80% [[14](#_ENREF_14)]. Hence, we aim to have a total of 2,200 participants recruited into the study. Given the prevalence of Fabry disease in dialysis population estimated to be 0.3% [[11](#_ENREF_11)], there will be approximately 7 patients with Fabry disease in our study population. However, screening was mainly done using alfa-galactosidase enzyme test, which is not reliable in diagnosing female patients with Fabry disease. Using alfa-galactosidase enzyme, Lyso-GB3 and GLA genetic tests, SoFAH study aims to provide more accurate prevalence rate of Fabry disease amongst the haemodialysis population in the UK.

**8.2 Planned recruitment rate**

We aim to recruit 70 participants per week across all sites over 12 months. Seven research nurses working at 2 days per week will be involved in the recruitment. Each will aim to recruit 10 patients per week.

**8.3 Statistical analysis plan** *(see under 10.3.3)*

* + Descriptive statistics will be used to assess prevalence of Fabry disease and secondary objectives
	+ Cost-effectiveness analysis of screening for Fabry disease among an unselected population of haemodialysis patients based on the outcome of the descriptive screening study.

**8.3.1 Summary of baseline data and flow of patients**

 Demographic and clinical data of the participants, , which include age, gender, ethnicity, clinical symptoms associated with Fabry disease, cardiovascular history, previous renal diagnosis, previous renal biopsy report and dialysis vintage, are collected via renal database and electronic patient medical record after enrolment.

All participants are asked to complete a Fabry disease symptoms paper questionnaire and EQ5D-5L paper questionnaire during dialysis. Participants with language barrier, or unable to read or write in English can have help from research nurses or haemodialysis nurses in order to complete the forms.

 (Please refer to Figure 1.0 for flow of patients)

**8.3.2 Primary outcome analysis**

The primary outcome of the prevalence of Fabry disease in haemodialysis population will be reported using descriptive statistics.

**8.3.3 Secondary outcome analysis**

The secondary outcomes on genetic and clinical characteristics of new cases of Fabry disease identified in the study will be reported using descriptive statistics.

 Comparative analysis of demographic and clinical differences between patients with Fabry disease and those without Fabry disease in the study population will be performed using SPSS.

Numerical values are expressed as mean (standard deviation) for parametric data or median (interquartile range (IQR)) for non-parametric data. Non-parametric variables will be log transformed prior to analysis to achieve normal distribution or, if this is not achieved, variables will be analysed using non-parametric test. Categorical values will be presented as percentage (number of participants). Parametric continuous data will be compared by means of student t-test, whilst non-parametric continuous data were compared using Mann-Whitney test. Categorical data will be compared by means of χ2 test. Statistical significance is defined as two-tailed p value <0.05.

**8.4 Subgroup analyses**

 None

**8.5 Adjusted analysis**

 None

**8.6 Interim analysis and criteria for the premature termination of the trial**

None

**8.7 Subject population**

 All consented participants will be recruited into the study.

**8.8 Procedure(s) to account for missing or spurious data**

In the case of missing enzyme or lyso-GB3 results, participantswill be asked if they agree for repeat blood sampling on their next haemodialysis session.

 Research nurses at each site will ask patients via telephone or face-to-face for any missing data on their demographics or clinical symptoms. Principal investigators will be involved to facilitate the completeness of the clinical data of their recruited participants to minimise missing data.

 The reasons for any missing data are to be documented in the case report form.

 Missing data will be excluded from the analysis.

**8.9 Other statistical considerations.**

**8.9.1 Economic evaluation**

Given budgetary constraints, any health care investment requires evidence of value for money to inform guideline development and ensure uptake by clinicians. An economic evaluation will be conducted from the perspective of the health and personal social services care provider in England. The evaluation will follow the NICE reference case for technology appraisals and as such the primary endpoint will be cost per quality-adjusted life year (QALY) over a lifetime horizon.

We will compare the cost-effectiveness of Fabry disease screening strategies vs. usual care (no screening). We will develop a decision-analytic model, mapping out the patient pathway and estimating lifetime costs, benefits and harms of the screening strategies. The model will be developed with patient and clinician input but is likely to include screening costs, early intervention with enzyme replacement therapy, prevention of kidney disease progression and dialysis and cardiovascular disease. We will use data from the proposed observational study to inform diagnostic yield and Fabry disease complication rates. These will be supplemented by targeted literature reviews.

We will conduct analyses to extend the evaluation beyond the incident patient to family members who could benefit from early treatment following diagnoses in cascade screening. We will estimate the budget impact of rolling out the screening strategies.

We will conduct extensive one-way and scenario sensitivity analyses to identify key drivers of cost-effectiveness and areas of uncertainty. We will conduct probabilistic sensitivity analyses (PSA) to characterise parameter uncertainty and present results in terms of incremental cost-effectiveness ratios (ICERs), cost-effectiveness acceptability curves and net-benefit distributions.

#

# 9. AUDIT & MONITORING

The study may be monitored and/or audited by University Hospitals Birmingham NHS Foundation Trust under their remit as Sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice and the UK Policy Framework for Health and Social Care Research.

Monitoring of study data shall include confirmation of subject eligibility and informed consent; adherence to the study protocol, source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. Study conduct will be subject to systems audit of the trial master file for inclusion of essential documents; permissions to conduct the trial; study delegation log; CV.s of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs. The Sponsors QA Manager, or a nominated designee of the Sponsor, shall carry out monitoring of study data as an on-going activity.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

# 10. STUDY MANAGEMENT

The conduct of the research will be overseen by the Chief Investigator and a representative of the Sponsor from University Hospitals Birmingham NHS Foundation Trust. The Sponsor representative will report into the R&D Management Team on progress of the trial, in line with the Trust’s standard operating procedures for Sponsorship.

The trial management committee (membership detailed in the administrative information on page 4 & 5) will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

# 11. REGULATORY APPROVALS

Approvals will be obtained from the Research Ethics Committee (REC) prior to the commencement of this study. Confirmation of Capability and Capacity will be obtained from the relevant Trust prior to any research activity being undertaken. The study will be conducted in accordance with principles of the International Committee on Harmonisation and Good Clinical Practice Guidelines.

## **11.1 Sponsorship and Indemnity**

University Hospitals Birmingham NHS Foundation Trust will act as the Sponsor to this study. Delegated responsibilities will be assigned to the Chief Investigator. University Hospitals Birmingham NHS Foundation Trust holds standard NHS Hospital indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

# 12. DISSEMINATION POLICY

The findings of this study will be reported at appropriate conferences and the aim is to publish them in a relevant open access journal. A summary report will be produced adherent to the funder’s guidelines at the completion of the project. Participants in the study will also be informed of the study outcome via a letter.

**13. REFERENCES**

1. Mahmud HM: Fabry's disease--a comprehensive review on pathogenesis, diagnosis and treatment. JPMA The Journal of the Pakistan Medical Association 2014, 64(2):189-194.

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**14. Appendices**

**Appendix 1**

