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FULL TITLE OF THE STUDY: Understanding beta cell disorders through the study of rare genotypes

SHORT STUDY TITLE &/or ACRONYM: ENDURE

PROTOCOL VERSION NUMBER AND DATE	**Version 2.0** 01 May 2024
RESEARCH REFERENCE NUMBERS AND DATES IRAS REC SPONSOR Protocol Reference NIHR Exeter Clinical Research Facility	 340277 24/NW/0117 23-24-21 CRF 580
FUNDERS Numbers	• Wellcome Trust Collaborative Award, 'Human-specific gene regulation in pancreatic beta-cell development' Ref: 224600/Z/21/Z • The Leona M. and Harry B. Helmsley Charitable Trust Type 1 Diabetes Program Grant Ref: R-2304-05983 • Diabetes UK and JDRF International RD Lawrence Fellowship Ref: 23/0006516
TRIAL REGISTRY NUMBER AND DATE ClinicalTrials.gov	 NCT06478121

This protocol has regard for the HRA guidance and order of content.

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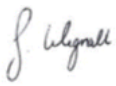
SIGNATURE PAGE

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 requirement.

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.

For and on behalf of the Study Sponsor:

Signature:  Date: 02/05/2024

Name: Suzy Wignall

Position: Senior Clinical Research Governance Manager

Chief Investigator:

Signature:  Date: 01/05/2024

Name: Professor Andrew Hattersley

Position: Professor of Molecular Medicine

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KEY STUDY CONTACTS

Chief Investigator	**Professor Andrew Hattersley** Professor of Molecular Medicine University of Exeter Medical School RILD Level 3, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 408260 Direct Mobile: +44 (0) 7973 165924 / PA Tel: +44 (0) 1392 408231 Email: A.T.Hattersley@exeter.ac.uk
Co-Investigators	**Dr Kashyap Patel** (Deputy CI) Wellcome Trust Career Development Fellow Consultant in Diabetes & Endocrinology University of Exeter Medical School RILD Level 3, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0)1392 408256 Email: K.A.Patel@exeter.ac.uk **Dr Martin Eichmann** Lecturer in Immunology University of Exeter Medical School RILD Level 4, Barrack Road, Exeter EX2 5DW, UK Email: M.Eichmann@exeter.ac.uk **Dr Matthew Johnson** Senior Research Fellow University of Exeter Medical School RILD Level 3, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 408277 Email: M.Johnson@exeter.ac.uk **Professor Sarah Flanagan** Professor of Genomic Medicine Wellcome Trust Senior Research Fellow University of Exeter Medical School RILD Level 3, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0)1392 408323 Email: S.Flanagan@exeter.ac.uk **Dr Elisa De Franco** Senior Research Fellow University of Exeter Medical School RILD Level 3, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 408232 Email: E.De-Franco@exeter.ac.uk

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SPONSOR SPONSOR REPRESENTATIVE	**University of Exeter** Generic Sponsor mailbox: res-sponsor@exeter.ac.uk **Suzy Wignall** Senior Clinical Research Governance Manager Research Ethics and Governance Office University of Exeter Lafrowda House, St Germans Road, Exeter EX4 6TL, UK Tel: +44 (0) 1392 726621 Email: res-sponsor@exeter.ac.uk
NHS R&D CONTACT	**Lisa Treeby** Senior Network Research Facilitator Royal Devon University Healthcare NHS Foundation Trust R & D Room F5, Bowmoor House, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 403814 Email: Lisa.Treeby@nhs.net
Study Co-ordination Project Manager Project Administrator	**Michelle Hudson** Research Project Manager NIHR Exeter Clinical Research Facility RILD Level 2, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 408181 Email: M.Hudson@exeter.ac.uk **Rebecca Dobbs** Graduate Research Assistant NIHR Exeter Clinical Research Facility RILD Level 2, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 408181 Email: R.A.Dobbs@exeter.ac.uk
Funder(s) NIHR Support Infrastructure: NIHR Exeter Biomedical Research Centre (Exeter BRC) Director of NIHR Exeter Biomedical Research Centre	 Email: NIHRExeterBRC@exeter.ac.uk **Professor Sallie Lamb** Pro-Vice-Chancellor and Executive Dean, Faculty of Health and Life Sciences, Mireille Gillings Professor of Health Innovation Medical School Building, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU, UK Tel: +44 (0) 1392 725585 Email: S.E.Lamb@exeter.ac.uk

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NIHR Exeter Clinical Research Facility (Exeter CRF)	Tel: +44 (0) 1392 408181 Email: crf@ex.ac.uk
Scientific Director of NIHR Exeter Clinical Research Facility	**Professor Angela Shore** Professor of Cardiovascular Sciences and Scientific Director of NIHR Exeter Clinical Research Facility NIHR Exeter Clinical Research Facility, RILD Level 2, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 408181 Email: A.C.Shore@exeter.ac.uk
Mireille Gillings Neuroimaging Centre (MGNC)	Royal Devon & Exeter (Wonford) Hospital, Barrack Road, Exeter EX2 5DW, UK Email: mgnc@exeter.ac.uk
Statistician	**Dr Beverley Shields** Associate Professor in Medical Statistics University of Exeter Medical School RILD Level 3, Barrack Road, Exeter EX2 5DW, UK Tel: +44 (0) 1392 408203 Email: B.Shields@exeter.ac.uk

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STUDY SUMMARY

Study Title	Und**e**rsta**n**ding beta cell **d**isorders through the st**u**dy of **r**are g**e**notypes
Short Title and Internal ref. no.	ENDURE (CRF 580)
Study Design	Observational 'recruit by genotype' study The aim of this study is to gain greater insight into the cellular and molecular pathways underlying beta cell disorders and their physiological consequences, by studying individuals with a pathogenic genetic variant. We may compare these with a control cohort (without the variant of interest). Using a "recruit by genotype" approach will allow us to perform detailed and specific analysis according to the individual's genetic variant to gain relevant data on development and function of beta cells, alteration of immune cell features, and physiological parameters. We will create genotype-to-phenotype data that will improve our understanding of how beta cell disorders develop on a cellular and molecular level. Such information may enable identification of new drug targets, inform development of novel therapies to better treat people with beta cell disorders. A study visit will entail consent plus collection of height and weight measures, data, and blood samples for all participants. It may include optional procedure(s) dependent on genotype and sub-study objectives. There is no treatment and the participants' normal clinical care will be unaffected and will continue uninterrupted. A small subset of participants may be invited for further sub-studies in the future.
Study Participants	Participants are selected based on having a known rare causal genetic variant for a monogenic beta cell disorder, or identified as controls without the variant.
Main Inclusion Criteria	Presence/absence of a rare causal genetic variant in a gene associated with a monogenic beta cell disorder (e.g., diabetes, hyperinsulinism)
Planned Sample Size	We will study at least one individual for each respective rare genetic variant causal for a monogenic beta cell disorder (genotype of interest). Overall, in any one given year, we expect to study between 5-25 participants.
Planned Study Period	From 1st June 2024 – 31st March 2029
Objectives	To identify and describe biomarkers and cellular features in blood samples that occur because of the rare causal genetic variant. To study the altered physiology or cellular function that are due to the rare causal genetic variant.
Outcomes	Identification and description of biomarkers or cellular features associated with specific rare causal genetic variants. Identification of alterations in physiological function with specific rare genetic variants.

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FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Wellcome Trust Collaborative Award, 'Human-specific gene regulation in pancreatic beta-cell development' Ref: 224600/Z/21/Z Awarded to: Andrew Hattersley Duration: 1st April 2022 – 31st March 2027	£3,500,000
The Leona M. and Harry B. Helmsley Charitable Trust Type 1 Diabetes Program Ref: R-2304-05983 Awarded to: Martin Eichmann Duration: 1st Sep 2022 – 31st Aug 2025	£312,221 ($316,265)
Diabetes UK and JDRF International RD Lawrence Fellowship Ref: 23/0006516 Awarded to: Matthew Johnson Duration: 1st Apr 2024 - 31st Mar 2029	£525,000
Research & Development Directorate, Royal Devon University Healthcare NHS Foundation Trust	Site-level Support
NIHR Exeter Clinical Research Facility	Support Infrastructure
NIHR Exeter Biomedical Research Centre	Support Infrastructure

ROLE OF STUDY SPONSOR AND FUNDERS

The University of Exeter is the sponsor of the ENDURE study and assumes overall responsibility for the initiation and management of the study and responsibility for monitoring of the study site.

The sponsor will review and approve the study protocol and any supporting documents.

The sponsor and the funders had no role in the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

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ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT

The Study Management Group (SMG)**,** to include the CI, Co-investigators, Project Manager and Project Administrator, will meet/communicate regularly to ensure all practical details of the study are progressing and working well. Clinical support will be provided by the NIHR Exeter Clinical Research Facility.

There will be no overall steering committee because the specific objectives and outcomes are defined by the specific rare genetic subtypes studied. However, to allow for scientific exchange and input, the CI and Co-Is meet regularly as part of the Exeter Centre of Excellence in Diabetes Research (ExCEED).

PROTOCOL CONTRIBUTORS

The sponsor and the funders had no role in the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

We have introduced this study to the Peninsula Research Bank (PRB) and Exeter Diabetes Patient and Public Involvement and Engagement (PPIE) groups and have incorporated feedback into the development of the study protocol, participant information sheets, flowcharts, and consent/assent forms.

KEY WORDS

Beta cell disorders	Monogenic diabetes	Hyperinsulinism
Causal genetic variant	Genotype-to-phenotype	Cellular and molecular analysis

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ENDURE Study – Summary Diagram

Identification of Participants

Individuals with a genetic variant of interest (causal for a monogenic beta cell disorder) are identified from our existing cohorts.

⇩

Pre-visit

Potential participants will be approached and provided with the appropriate study information leaflet and other study documents.
Follow up contact will be made to discuss the study and answer any questions.
Study visit will be arranged.

⇩

Visit

Visit procedures according to participant's genotype.
Visit duration: 40 minutes to 2 hours.

Written informed consent

Core Study :

- Data collection (anthropometric, clinical)
- Blood collection

Imaging Sub-Study (according to genetic variant studied):

- Magnetic Resonance Imaging (MRI) scan

A small subset of participants may be invited for further sub-studies in the future.

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STUDY PROTOCOL

Understanding beta cell disorders through the study of rare genotypes (ENDURE)

1 BACKGROUND (Introduction)

Insulin is the only hormone in the body that reduces blood sugar levels. Insulin is produced in cells in the pancreas, called beta cells. The development and function of beta cells is tightly regulated.

In diabetes the blood sugar is raised. This is most often caused by a reduction or absence of insulin. Lower or absent insulin is caused by beta cells not developing correctly, functioning properly, or being destroyed. If there is too much insulin, known as hyperinsulinism, the blood sugar goes too low. Hyperinsulinism is caused by over production of insulin by the beta-cells.

In rare cases, referred to as monogenic disease, beta cell disorders can be caused by a single genetic variant. The University of Exeter research team have played an important role in identifying many of the genetic causes of both diabetes and hyperinsulinism [1]. The identification of genetic determinants allows patients with monogenic diabetes to be diagnosed and sub classified. In many cases we need to understand better the functional and physiological consequences of the genetic variants that ultimately lead to disease.

Monogenic Diabetes where diabetes is caused by a single genetic variant affects approximately 1 in 10,000 of the population. Monogenic Diabetes is typically diagnosed under the age of 30 years but can occur in the first few days of life. The very young cases diagnosed in the first 6 months of life are known as neonatal diabetes which is caused by beta cells not developing properly, not functioning correctly, or being destroyed [2]. Understanding how the genetic variants cause monogenic diabetes may allow for better understanding of the development, and function of the human insulin producing beta-cell. In addition, studying participants with neonatal diabetes where diabetes occurs shortly after birth (due to a lack of insulin), can allow us better insight into the role of insulin in human physiology [3].

Hyperinsulinism (HI), is a rare beta cell disorder, affecting 1/10,000-1/25,000 live births. HI is characterised by excessive secretion of insulin leading to a low blood glucose level. Most cases with permanent HI are caused by genetic variation in a single gene. Identifying and understanding the genetic cause is important for the better management of patients and improved understanding of the normal beta-cell.

Exeter is an international referral centre for genetic testing of monogenic beta cell disorders, and we have identified genetic causes in over 8,000 patients from over 100 countries. We now wish to study some of these individuals in more detail to understand how these genetic variants affects:

a) beta cell development and function.

b) immune cell properties and function.

c) human physiology.

Studying individuals with rare forms of disease can offer unique insights into common forms of disease by acting as a ‘human model’ system. The insights gained from studying rare genetic beta cell disorders have crucial importance for the understanding of common forms of diabetes (Type 1

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diabetes and Type 2 diabetes) by providing new information on beta-cell development, function, and human physiology.

Our study aims to provide novel insights of underlying mechanisms, pathological features, and novel therapeutic avenues by studying people with rare genetic mutations causing beta cell disorders. We hope this information will help scientists to tackle Type 1 and Type 2 diabetes.

ENDURE study website: https://www.diabetesgenes.org/current-research/endure-study/

1.1 Lay Summary

The human body needs sugar for energy, but too much or too little sugar in the blood is bad for us. To control the amount of sugar in the blood, a molecule called insulin is made by specialised beta cells in the pancreas. In diabetes, beta cells don't make enough insulin which causes high blood sugar levels. In hyperinsulinism, they make too much insulin leading to very low blood sugar levels. Over time, these disorders can lead to serious health problems.

The cause of some cases of diabetes and nearly all cases of hyperinsulinism, is a single spelling mistake in the person's DNA (a variant) that changes how the insulin producing beta cells work. By studying these people, we can get new information about how beta cells work.

The overarching aim of the ENDURE study is to understand how DNA variants cause beta cell disorders. The exact aims of the study will vary depending on the specific genetic variant and we will ask participants to agree to specific procedures that will allow us to determine one or more of the following aims:

a) to gain a better understanding of the underlying mechanism(s) that:
- lead to beta cells not functioning correctly.
- result in the destruction of beta cells by immune cells.

b) to gain better understanding of how specific beta cell disorders affect physiology (how the body functions).

Participants will be selected based on having a confirmed disease-causing genetic change that results in beta cells not working properly. All people who consent to take part in the ENDURE study will take part in the Core Study. We will collect clinical data and blood samples (collected via the method used in normal healthcare) for us to do specialist analyses to understand the consequence of the genetic variant. The Core Study visit will usually take 40-60 minutes.

Depending on the person's genetic change, they may be asked to take part in the Imaging Sub-Study where participants will be asked to have an MRI (Magnetic Resonance Imaging) scan to enable us to better understand how the genetic change affects how the body works. The scans will be performed at the Mireille Gillings Neuroimaging Centre (MGNC) located at the hospital site. The images will measure organ size (eg liver and pancreas), percentage liver fat, and body fat distribution. The MRI appointment will usually take an extra 40-60 minutes and may be arranged as a separate visit if more convenient for the participant. To help us increase our understanding of how the beta cell works, we will also invite and study people of the same sex, who are close in age and weight and do not have the genetic change. This will help us to find differences between them.

The overall outcome of our research will be to improve understanding of how beta cells work. We hope that the insights from this research may lead to new ways to treat and/or improve the lives of people living with beta cell disorders.

ENDURE study website: https://www.diabetesgenes.org/current-research/endure-study/

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2 RATIONALE

Studying individuals with a monogenic beta cell disorder caused by a distinct pathogenic single genetic variant will allow us to study and define the direct effects of the genetic variant on cellular and molecular function, specifically how this affects beta cell development, function, and destruction. A clear description of effects may enable us to refine our understanding of beta cell development and function and may allow us to improve disease management.

Monogenic beta cell disorders are rare, where a single alteration in a pathway leads to disease. They can therefore be described as extreme cases of polygenic beta cell disorders where multiple pathways are slightly dysfunctional and these multifactorial alterations lead to disease. Study of the monogenic disorder will allow us an unprecedented insight into how more common beta cell disorders develop, particularly regarding how the immune system interacts with beta cells.

3 THEORETICAL FRAMEWORK

Study of individuals with a rare causal genetic variant in a gene associated with a monogenic beta cell disorder will allow the researchers to identify underlying mechanisms and properties that will further our understanding of function, physiology, and pathogenesis.

The following specific aims will be addressed within the scope of the ENDURE study:

1) Wellcome Trust Collaborative Award, 'Human-specific gene regulation in pancreatic beta-cell development' Ref: 224600/Z/21/Z
   Aim of subproject "to identify the impact of absence of insulin in utero on long term growth and metabolism".

2) The Leona M. and Harry B. Helmsley Charitable Trust, Type 1 Diabetes Program Ref: R-2304-05983
   Aim: To define how molecular features of insulin recognition in the immune system are affected in individuals lacking endogenous insulin.

3) Diabetes UK and JDRF International, RD Lawrence Fellowship Ref: 23/0006516
   Aim: To identify and characterise new genetic forms of autoimmune diabetes (a monogenic beta cell disorder) to uncover new mechanisms of beta cell destruction.

4 RESEARCH QUESTION/AIMS

4.1 Aim

The ENDURE study aims to improve our understanding of the molecular and physiological mechanisms that underlie beta cell disorders by studying individuals with a pathogenic genetic variant.

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4.2 Objectives

- To identify and describe biomarkers and cellular features in blood samples that occur because of the rare causal genetic variant.
- To study the altered physiology or cellular function that are due to the rare causal genetic variant.

4.3 Outcomes

- Identification and description of biomarkers or cellular features associated with specific rare causal genetic variants.
- Identification of alterations in physiological function with specific rare genetic variants.

5 STUDY DESIGN and DATA ANALYSIS

5.1 Study Design

The ENDURE study is an observational “recruit-by-genotype” case (series) study and will be conducted initially over a period of 5 years (2024 to 2029).

Participants will be selected for testing based on having a confirmed causative variant associated with a monogenic beta cell disorder (‘genetic subtype’), or being identified as a suitably matched control.

To study each genetic subtype, we will recruit different participants and perform specific study procedures and tests (see Appendix 4 – Study Flowcharts) to achieve our objectives. This protocol has, therefore, been written to describe a Core Study relevant to all participants, with additional sub-studies depending on the specific genetic subtype and research aims.

We have aimed to reduce the governance burden by setting out a combined application supported by several separate funding sources that all relate to improving understanding of beta cell disorders.

Since the general management and ethical issues are overarching, as new genetic subtypes are identified over the study period, approval will be sought for specific sub-studies via amendments, rather than submitting each cohort as a separate ethics application. Our approach will, therefore, continue to avoid an unacceptable governance burden on both researchers and ethics committees.

All participants will have data collected and donate blood samples. Some participants, according to their genotype, will be invited to take part in a separate Sub-Study (e.g., Imaging Sub-Study), to have additional procedure(s), as outlined in the Sub-Study Flowchart (e.g. Imaging Sub-Study Flowchart).

This study design follows the ‘recruit by genotype’ study *Diabetes Variants* (DIVA) (IRAS: 167199, REC:14/SW/1140), conducted by the NIHR Exeter CRF (2014-18) and allows for the addition of sub-studies in the future via amendments.

5.2 Study Timeframe

Some genotype-to-phenotype studies may be completed in a short timeframe and novel genetic variants will likely be discovered and then studied within the ENDURE study remit. Therefore, recruitment, testing, analyses and writing up of the findings of genotype-to-phenotype studies may continue throughout the ENDURE study period.

Milestones		*Years 1-4*	*Year 5*	
	6 m *Oct 23 – May 24*	*June 24 – Mar 28*	*Apr 28 - Sept 28*	*Oct 28 – Mar 29*
Ethical/Governance approvals & work-up				
Recruitment				
Follow-up tests				
Data collection				
Sample batched analysis				
Data analysis				
Writing up / future funding applications / publications				

5.3 End of Study Definition

The parameter marking the end of the study is the 3 months after the final participant's final visit or 3 months prior to end of the funded period (whichever is later), to allow for final collection of data and analysis.

5.4 Data Collection and Recording

Data protection and patient confidentiality are covered in section 9.6.

All participants will be pseudo-anonymised by assigning a unique study ID under which all data and samples collected will be recorded and stored. Data will be initially recorded using a study-specific case report form (CRF), with hard copies stored in the Trial Master File (TMF). Anonymised research data will be recorded on a study-specific password protected database stored on a secure NHS server. Exeter CRF data quality procedures require data collected and recorded to be screened and reviewed for discrepancies and missing data prior to analysis.

Data to be collected will include:

- Personal identifiers: Full Name, Contact information (address, email), NHS number (where applicable).
- Diabetes & other significant medical history, including current diabetes medications.
- Anthropometry: including Height (m), Weight (Kg), will be recorded.

Case Report Form (data collection form)

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The relevant visit Case Report Form (CRF) will capture all the information required to ensure that all the documented statistical information dictated in the protocol is captured and documented at each visit. This also serves to monitor patient eligibility and safety at Sponsor level.

6 SAMPLES and TESTING

6.1 Sample Laboratory Testing

Obtained samples will either be tested in the Co-I's laboratory or at dedicated clinical laboratories at the Exeter Blood Sciences Laboratory at the Royal Devon University Healthcare NHS Foundation Trust site, as outlined below.

Investigators will usually make use of the University of Exeter core facilities for downstream analysis, but some testing may have to be performed using an external service (within or outside the UK), either NHS, academic, or commercial. All internal testing and analysis will be conducted by a suitably qualified and trained member of the research team, whose role is documented on the study delegation log. A detailed SOP will be available to follow for each test performed internally.

6.2 Sample Collection, Labelling and Logging

All samples will be collected and processed by a suitably qualified and trained member of the clinical/research team, whose role is documented on the study delegation log. A detailed SOP/work instruction will be provided detailing the clinical procedure for collecting the sample(s) and the logistics of sample labelling, logging, and management and transfer to the relevant laboratory for analysis. All study-specific procedures will be covered during the Site Initiation Visit.

6.3 Laboratory Assessments and Results Reporting

The Exeter Clinical Laboratories have an established pipeline for receiving and processing all research samples, including documentation of chain of custody. Central laboratory analysis of the study samples will be undertaken at the Exeter Blood Sciences Laboratory at the Royal Devon University Healthcare NHS Foundation Trust site. Upon receipt, the specimens will be assessed for content and integrity. The samples will be logged immediately, and all samples will be tracked using the laboratory information management system (LIMS).

The Exeter Blood Sciences Laboratory will provide analyses from routine biochemistry tests available in the NHS test repertoire. All assays are CE marked, fully validated, and accredited by CPA (Clinical Pathology Accreditation). Clinical results will be available within 21 days of receipt of the sample.

6.4 Investigators' Laboratories

The Investigators' laboratories, based at the University of Exeter, will receive blood samples to isolate blood fractions according to established protocols according to manufacturers' description. This work will be conducted by a suitably qualified and trained member of the research team, whose role is documented on the study delegation log. A detailed SOP will be provided detailing clear instruction to the logistics of sample labelling, logging and management of sample processing and storage of isolated blood fractions.

The participant's genotype will determine which blood fractions will be isolated. Blood samples will be obtained to separate out the cellular (peripheral blood mononuclear cells) and acellular (plasma or serum or RNA/DNA) fractions to perform subsequent measurements on these fractions.

Downstream testing and analysis of blood fractions will include a selection or combination of tests such as:

- Fluorescence-activated cell sorting (FACS)
- Immune phenotyping via flow cytometry
- Isolation of DNA/RNA from defined cell populations
- Epigenetic array analysis
- Gene expression analysis
- Functional assay on (isolated) cell subsets (including but not limited to co-culture, ELISA, ELISpot)
- Alternative testing, as required

Equipment is regularly serviced and maintained to manufacturers' instructions.

While the majority of tests and analysis will be performed at the University of Exeter, in some cases, we will use fee-for-service providers, or academic collaborators, to perform some of tests.

6.5 Sample Storage

Robust procedures, in compliance with the Human Tissue Act 2004, are always followed to monitor and maintain the integrity and traceability of the samples, stored in a licensed area, including their disposal. All samples will be processed, logged and frozen using sample-appropriate storage procedures. HTA approved locations for storage are available within the Investigators' laboratories at the University of Exeter Medical School. All saved samples will be stored under the study ID, with the file linking the study code to personal identifiable information held securely by the PI, accessible only to personnel with training in data protection who require this information to perform their duties. Those with access to personal identifiable data will be documented on the study Delegation Log.
All samples sent to the Exeter Clinical Laboratories must be logged on the study sample database. The Study ID will provide a robust pseudo-anonymised system for management and location tracking of all study samples. The research team will monitor consent status via the study database. Where samples are unable to be collected, this should be documented under the participant Study ID with reason for non-collection provided.
Transfer of custodianship of stored samples with consent to the Genetic Beta Cell Research Bank (GBCRB), managed by The Royal Devon University Healthcare NHS Foundation Trust's Exeter Genomics Laboratory, may occur during the study or at the end of the study as defined above. Stored samples will then be made available for further separate ethically-approved research.

7 STUDY SETTING

The ENDURE study is an observational study run at a single NHS site study, with the University of Exeter as Sponsor. The Exeter Clinical Laboratories encompass the Exeter Genomics Laboratory and Exeter Blood Sciences Laboratory at the Royal Devon University Healthcare NHS Foundation Trust (Royal Devon). The Exeter Genomics Laboratory is a worldwide referral centre that tests DNA samples from patients to diagnose or predict genetic disease and to guide clinical care. Exeter Blood Sciences Laboratory is a clinical diagnostic facility.

Participants will be recruited via the NIHR Exeter Clinical Research Facility (Exeter CRF) and ENDURE study team (CI, Co-I and designated Project Manager and Administrator). Sample

collection will be performed by CRF staff in the Exeter CRF or possibly at another location if more suitable and convenient for the participant.

MRI imaging will usually be performed at the Mireille Gillings Neuroimaging Centre (MGNC) which provides state of the art MRI scanning facilities for research, clinical diagnosis, and therapy. The Exeter CRF and MGNC are partnerships between the University of Exeter and Royal Devon University Healthcare NHS Foundation Trust, and are located at the Royal Devon and Exeter (Wonford) Hospital in Exeter.

All study participants will be invited to the Exeter CRF (or alternative convenient location) to provide written informed consent/assent and undergo Core Study data collection, measurements, and provide blood samples collected by a nurse or doctor (paediatric, if necessary), fully trained in this procedure. This Core Study visit should take approximately 40 minutes to 1 hour.

Depending on their genotype, participants are invited to take part in the Imaging Sub-Study to have an MRI (Magnetic Resonance Imaging) scan to measure organ size and body fat distribution [4]. The scan will be performed at the Mireille Gillings Neuroimaging Centre and will usually take 40-60 minutes. The MRI appointment may be arranged as a separate visit if more convenient for the participant.

The study team will undertake every effort to ensure that the duration of the study visit, for the participant to undertake all procedures, is kept to a minimum.

Prospective study participants will be provided with the appropriate participant information sheet (PIS) and Sub-Study Flowchart detailing the study and procedures (specific to the participant's genotype) . If interested in participating, the ENDURE study team will contact them to discuss the study in detail and answer any questions and address concerns raised to allow the prospective participant to make an informed decision regarding taking part in the study. For the Imaging Sub-Study, following receipt of verbal consent, we will ask the participant to complete and provide the "MRI Safety Checklist Screening Form" that is necessary to screen them prior to booking their MRI scan. Prospective study participants are individuals with a rare genetic mutation that is associated with a monogenic beta cell disorder. The cohort of prospective study participants is diverse in terms of background, primary language, home country. To have an inclusive study set-up, we will:

1) provide documents that are translated into the participant's (or guardian's) primary language, where English is not the primary language. Additionally, an NHS appointed interpreter/interpretation service (e.g., Language Line) will be arranged for phone calls and the study visit to ensure clear communication. The participant's clinician may also attend and provide translation.
2) support/arrange and reimburse/pay (according to standard University of Exeter policy) for travel/accommodation/subsistence to facilitate the participant's [including guardian(s)] ability to participate in the study. For participants travelling from outside of the UK, we may use a travel agent to provide a service to the participant to minimise travel associated burden (organisation, re-imbursement, etc.).

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8 PARTICIPANT SELECTION

8.1 Eligibility Criteria

8.1.1 Inclusion criteria

Participants will have:

- Adult: mental capacity to give informed consent
- Child: parent/guardian has mental capacity to give informed consent, and child has capacity to give assent (which will be provided in an age-adjusted format).
- any sex, ethnicity, location.

Eligibility to have a different procedure is age dependent, as outlined below.

Core Study: Blood collection - 6 years of age and older

Imaging Sub-Study: MRI scan: 6 years of age and older

Specific inclusion criteria

Group 1: case participants:

- Known to have a genetic variant(s) resulting in a beta cell disorder.

Group 2: healthy controls:

- Not known to have a genetic variant(s) resulting in a beta cell disorder.
- Matched for age (+/- 15%)
- Matched for BMI (+/- 3 kg/m^2).

8.1.2 Exclusion criteria

Exclusions for Core Procedure:

- Adult: lacks mental capacity to give informed consent
- Child: parent/guardian lacks mental capacity to give informed consent
- Blood collection - age <6 years or age >99 years

Exclusions for MRI assessments:

- Age <6 years or age >99 years
- Cochlear Implant; Aneurysm Clips; Neurological stimulator; Implanted cardiac devices (ICD, PPM, loop recorders, or any others); Metal heart valve; History of metal foreign bodies in orbits; Other implanted metal device which prevents MRI
- Known claustrophobia.

8.2 Participant Number

We will study at least one individual for each respective rare genetic variant causal for a monogenic beta cell disorder (genotype of interest). Overall, in any one given year, we expect to study between 5-25 participants.

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8.2.1 Statistical considerations

Case-Control Study

Case-Control studies will be explicitly listed here. Additions Cohorts/Sub-studies will be requested and approved via an amendment.

For substudies that are case-control studies, different numbers of participants will be required. We will perform independent sample size and power calculations to determine if we are likely to be able to recruit and test the required number of participants.

Case-Control Study (e.g, Imaging Sub-Study): ('Human-specific gene regulation in pancreatic beta-cell development' Ref: 224600/Z/21/Z)

Statistical Consideration and Feasibility:
We need the power to detect a mean difference of 1 standard deviation in outcome measures of physiological function between monogenic cases and matched controls of the same sex and similar age and BMI (that do not have the condition). For this magnitude of difference, with 90% power, alpha=0.05, we would need to study 22 cases and 22 controls.

In our monogenic diabetes cohort, we have 361 individuals in the UK eliqible for this case-control study (i.e. with a rare variant leading to lack of insulin in utero), so we are confident that we will be able to recruit the required number of cases.

Prospective healthy control individuals may be family members of participants (through the Genetic Beta Cell Research Bank), or via application to the Peninsula Research Bank (PRB). The PRB includes Exeter 10,000 study (EXTEND) involving ~11,000 volunteers (≥ 16 years of age) with consent to contact for further research. We are confident that we will be able to recruit the required number of matched healthy controls.

Case Study

Feasibility:
This is an exploratory case observation study, with no direct comparator group, and as such no formal sample size calculation is possible nor required.
For some studies recruiting even a single patient is sufficient because of the uniqueness of the patient due to their genetic variant. In these cases, a single observation will confirm a scientific principle and equally the absence of that observation will question the scientific principle.

8.3 Recruitment and Visit Procedures

8.3.1 Participant identification

The Co-Investigators will select and study individuals that have an identified rare pathogenic genetic variant that leads to a beta cell disorder.

Prospective case individuals will be identified using the University of Exeter monogenic diabetes cohort and its clinical links and recruitment will be facilitated via the Exeter CRF and the study team.

There are two approaches following initial identification, depending on whether the prospective participant has given consent in the past to be contacted about potential research studies.

A) When there is prior consent to contact about research: the research nurse/researcher will contact the prospective participants directly by phone/email/letter (as per the previously recorded

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preference of that individual) and will provide them with the study information sheet to read, prior to starting the consent process.

B) When there is no prior consent to contact the individual directly: the Exeter team member, who provided the diagnostic clinical test results to the individual's clinical team, will inform the clinical team about the study. If considered appropriate by the clinical team, they will provide the patient with details of the research and ask them if they would like to hear more about the study and be contacted by the research team directly.

Control identification:

In addition, we will study sex-matched healthy controls with similar age and BMI (age: +/-15%, BMI: +/- 3 kg/m^2) for specified case-control studies.

Prospective healthy control individuals may be family members of participants or identified via the Genetic Beta Cell Research Bank, or the Peninsula Research Bank (PRB). These will be recruited, either because they have given prior consent to be contacted for future research or, when an individual with a beta-cell disorder has consented to take part, we will ask if any other family members would like to be controls.

8.3.2 Consent

Identified individuals, and their parent/guardians where required, will be provided with the study information sheet, consent form, and contact details of the study team. A member of the study team (usually Exeter CRF Research Nurse) will contact them to explain what the study entails and answer any questions they have. If interested in participating, the researcher will check eligibility. If they agree to take part, verbal consent will be sought to participate and for their information to be stored, and an appointment will be made and confirmed in writing by email/letter. The verbal consent process involves the research nurse/doctor/researcher and prospective participant/parent/guardian each recording the participant's answers on their version of the Consent Form over the telephone and dating it. The consent statements are re-checked at the start of the research visit, then signed and dated. As part of the consent process, potential participants, and/or their parent/legal guardian, will be assessed to check they have mental capacity to make an informed decision about study participation. They will be able to provide a brief overview of the study, procedures and potential risks and benefits of the study, demonstrating their understanding of what is involved. For the Imaging Sub-Study, following a telephone call and consent process, the research nurse will complete the "MRI Safety Checklist Screening Form" with the prospective participant which is necessary to screen them prior to booking their MRI scan. In addition to their name, date of birth, gender, contact details, and general health status being recorded for their appointment, information will be collected about implants, devices or objects that may be hazardous or may interfere with the MRI scan.

All participants recruited to the study (or their parent/guardian) will be required to give verbal informed consent (as described above) prior to any data collection. Written informed consent will be obtained at their research visit, prior to any study procedure. Where participants are between 6 and 16 years of age, they will be asked to give written informed assent prior to any study procedure. Participation will involve only a single study visit for the majority of participants. Should a child reach 16 years of age prior to a subsequent planned visit, we would seek their written consent to continue participation, using the Adult PIS and Consent Form. Prior to assent/consent, all potential participants will receive detailed written information (age-appropriate where necessary) about the study (that complies with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018), written in English and translated into the participant's/legal guardian's official language. There will be opportunity for the participants (and their legal guardian) to discuss any concerns or questions with the study team (in presence of a translator where required). In most cases, an Exeter

CRF Research Nurse will obtain consent and conduct the visit (with the exception of the MRI) but this may be done by a delegated doctor/researcher with appropriate training. As stipulated by GCP, participants will be provided with adequate time (at least 24 hours) to consider giving consent. It is the responsibility of the PI, or an appropriately trained and delegated individual, to receive written informed assent/consent from each participant following adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Informed consent should not be received until the participant is content that all questions have been adequately answered. Where translation is required, the routine NHS translation service will be used and/or the participant's clinician may attend and provide translation.

All participants (and their legal guardians) will be informed of their right to withdraw from the study at any time without prejudice or jeopardy to any future clinical care. When the sample is fully anonymised, the participants will still be able to withdraw but their samples and any data will be retained to be used in the analysis.

Withdrawal of consent
All participants (and their legal guardians) will be informed of their right to withdraw from the study, without stating a reason, at any time up to and including data and sample analysis, without prejudice or jeopardy to any future clinical care. If a participant permanently withdraws from the study, the reason (if provided) will be recorded.

Criteria for premature withdrawal from the study:

- Participant's withdrawal of consent.
- Investigators' discretion that it is in the best interest of the participant to withdraw.
- Termination of the study by the trial sponsor.

Where a participant withdraws, data will be collected up to the point of withdrawal in line with the protocol and study SOPs. If appropriate, the PI or delegated member of the research team will follow-up with the participant to ensure wellbeing and that ongoing clinical care is unaffected.

Where a participant has prematurely withdrawn but not revoked consent, data and samples will remain within the study and included in any analysis. Where consent is withdrawn, study samples and data will be kept/destroyed as per the following options, in line with data SOPs and local guidelines:

- samples and data remain.
- samples withdrawn; data remain.

Withdrawal will be recorded on the study database and the participant's choice of the above options recorded. A withdrawn participant is not obliged to give a reason for withdrawing their consent but, where they are willing to do so, the reason will be documented. Details of all withdrawn participants will be regularly reviewed to enable any study-wide trends relating to study procedures to be ascertained and acted upon where appropriate.

8.3.3 Visit Procedures

Following written consent to participate, all participants will undergo core data collection, height and weight measurements and provide blood samples.

Core Study – Blood collection (duration approximately 15 minutes)

At the research visit, blood sampling will be performed via venepuncture with adaption made according to age or participant. The amount of blood to be drawn from participants is solely for

research purposes and will not exceed the recommended limits in accordance with WHO guidelines according to age and/or weight of study participants; see Appendix 3. For children we will offer to use a topical anaesthetic, as is common practise during phlebotomy of children. Blood collection will be made into specific blood collection tubes according to the study aim.

Sub-Studies

According to the participant's genotype and related research question, participants may take part in Sub-Studies.

Imaging Sub-Study - Magnetic Resonance Imaging (MRI) (duration approximately 60 minutes)

Rationale: Patients with genetic variants that result in neonatal diabetes often lack insulin in utero as well as after birth. These patients are typically born at proximately half normal birth weight as the foetus in the womb lack insulin and this is a major growth factor for the foetus. To allow assessment of the impact of lack of insulin in utero on post-natal growth fat distribution and the pancreatic size we will image the patients with an MRI scan.

We will ask participants with genetic subtypes that stop insulin secretion in utero to have an MRI (optional) during their visit. This will take place at the Mirielle Gillings Neuroimaging Centre (MGNC).

MRI scan sequences will take images of the participant's body to look at fat distribution and measure organ size.

During the procedure the participant can ask to stop the procedure at any time, between and during scans; and can also have breaks between the scans. We will follow a priority scan list to obtain images according to importance to address the research questions.

We will use a CE marked MRI scanner to acquire multiple standard vendor sequences.

9 ETHICAL AND REGULATORY CONSIDERATIONS

This protocol and any subsequent amendments, along with any accompanying material provided to the participants, will be submitted by the Chief Investigator to an independent Research Ethics Committee (REC) and Health Research Authority (HRA). Written REC and HRA approvals will be obtained and subsequently submitted to the Sponsor R&D to obtain Sponsor approval prior to commencing the study. Local Trust's confirmation of capacity and capability will be in place before the Sponsor initiates the 'green light' for research activity to commence.

9.1 Safety Assessment and Management of Risk

9.1.1 Safety

Definitions and reporting of adverse effects (what should be reported?)

The timeframe for recording SAEs will be from the time of consent to one week following the last visit of a study participant. Any reportable adverse effects noted will be reported within 24 hours to the CI and the Sponsor as per standard NHS R&D protocols. Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site, or the PI at the participating sites. The Sponsor should be informed of these nominated individuals.

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Serious Adverse Event (SAE)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Reportable SAEs

ANY hospitalisation relating to phlebotomy procedure.

All reportable SAEs will be recorded in the participant's medical notes, the local Investigator Site File, and the Sponsor SAE form and reported to the Sponsor and CI/central coordinating team, within 24 hours of the CI or PI or co-investigators becoming aware of the event.

All non-reportable SAEs will be recorded in the participant's notes, and the CRF, but the Sponsor SAE form will not be filled out or reported to the Sponsor and CI/central coordinating team.

The following SAEs will be considered recordable but not reportable to the Sponsor:

- Hospitalisation for elective treatment.
- Hospitalisation for treatment of a pre-existing condition.
- Hospitalisation for non-diabetes related reasons.
- Hospitalisation due to road traffic accident.

9.1.2 Management of risk

BENEFIT:

Taking part in the study does not provide a direct healthcare or financial benefit to the participant.

Indirectly, participating in the study is likely to increase knowledge of their condition and may improve the lives of people with beta cell disorders in the future.

PROCEDURE RISK:

Core Study Procedure – Blood Collection:

Venepuncture is a standard and routine clinical procedure to draw blood that has limited risks associated. Any potential discomfort or side-effects will be equivalent to that experienced in routine clinical care. This procedure may result in slight bruising and discomfort. Risk will be minimised by the procedure being undertaken by an experienced clinician (nurse or doctor). To further reduce discomfort, particularly in children, local topical anaesthetic may be applied prior to venepuncture. We have made every effort to minimise the burden to the participant during their study visit.

Imaging Sub-Study Procedure – MRI Scan:

We will use a CE marked MRI scanner to acquire multiple standard vendor sequences. MRI is a painless procedure with no known risks to participants who fall within our inclusion criteria. However, it is noisy, and patients must lie still in a slightly confined space. Some people become claustrophobic being in the MRI scanner, which is detailed in the participant information sheet and we will discuss this with participants at the time of consent to minimise this risk. Should participants experience any discomfort during the scan, they will be able to alert the investigators immediately by activating an alarm and will be removed from the scanner immediately. Such feelings promptly subside as soon as the participant is out of the scanner. Participants will be provided with headphones to reduce noise and aid communication between participants and investigators.

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INCIDENTAL FINDINGS:

Investigations in this study are aimed to answer research questions and not guide clinical care. Therefore, individual results will not be reported routinely to the participant and their clinician(s). However, incidental findings outside the range of the normal population may occur. All incidental findings will be discussed with the CI, or medically qualified delegate, to assess whether immediate clinical action is required. If required, the test result(s) would be communicated back to the participant and their healthcare providers to enable initiation of follow-up and/or treatment.

Therefore, the research team will report to the CI all findings outside of the normal clinical range. The CI will determine if immediate clinical action is required and, if so, will contact the participant and their healthcare providers. Participants will not expect to receive individual results unless clinical action is needed. A statement to this effect is included in the information sheet and consent form.

9.2 Research Ethics Committee (REC) and other regulatory review & reports

Regulatory Review & Compliance

Before enrolling any participants into the study, the Chief Investigator/Principal Investigator or designee will ensure that a favourable opinion is in place from a REC and HRA, and appropriate approvals from participating organisations are in place.

Compliance

The CI will ensure that the study is conducted in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, other regulatory requirements, and any subsequent amendments.

Amendments

For any amendment to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body for them to review and issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so that they can put the necessary arrangements in place to implement the amendment and confirm their support for the study as amended.

9.3 Peer Review

Research aims and rationale of the studies to be conducted under this protocol have been reviewed favourably by extensive external peer review processes initiated by the study's funders, prior to awarding the grants.

9.4 Patient and Public Involvement (PPI)

The study team has access to the user representative group of the NIHR Exeter Clinical Research Facility (Exeter CRF) and the Exeter Diabetes PPI group. In keeping with the NHS Patient Carer and Public Involvement (PCPI) strategy, the Exeter CRF invites user representatives to contribute to the development of various projects within its portfolio. These individuals have agreed to maintain contact and regular meetings have been established at which researchers discuss the development of current projects within the Exeter CRF. The Exeter CRF user group and Exeter Diabetes PPI group have been actively involved in the study wording of the patient-facing documents for this study.

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9.5 Protocol Compliance

Monitoring

Monitoring of this study will ensure compliance with Good Clinical Practice. The Investigators will permit monitoring, audits, REC review, and regulatory inspections by providing the Sponsors, Regulators and REC direct access to source data and other documents (e.g., participants' case report forms, consent forms, etc.). Periodic remote monitoring will be conducted by the CI's study team and the Sponsor. Consent will be taken to permit access to data by external staff responsible for monitoring and auditing the study as a requirement of participating in the study. Remote monitoring of recruitment activities will be carried out periodically by the study management team (on behalf of the CI & Sponsor) by exploring data, consent forms, delegation log & recruitment log in accordance with the study SOPs/work instructions.

Serious Breaches in GCP or the Study Protocol

The CI is responsible for reporting any serious breaches to the Sponsor (R&D) within 24 hours.

Non-Compliance

Defined as a noted systematic lack of both the CI and the study staff adhering to SOPs/work instructions/protocol/ ICH-GCP and UK regulations, which leads to prolonged collection of deviations, breaches, or suspected fraud.

These non-compliances may be captured from a variety of diverse sources including monitoring visits, CRFs, communications and updates. The Sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The Sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the R&D will agree an appropriate action, including an on-site audit.

9.6 Data Protection and Patient Confidentiality

Confidentiality

The CI is responsible for ensuring that the participants' anonymity is protected and maintained, ensuring that their identities are protected from any unauthorised parties. The CI is the 'Custodian' of the data. All information related to study participants will be kept confidential and managed in accordance with the UK GDPR and Data Protection Act 2018, NHS Caldicott Guardian, UK Policy Framework for Health & Social Care, and Research Ethics Committee Approval.

A unique Study ID will be allocated to each participant. All study data and samples will be pseudo-anonymised and stored under the Study ID on a secure password-protected study database managed by the central coordinating team. Personal identifiable data will only be accessible to personnel with training in data protection who require this information to perform their study role. Personal data to be collected will include, name, date of birth, NHS or CHI number, gender, contact details and preferences. Identifiable information will be stored on a secure password-protected database held on an NHS server to enable the research team to undertake the study. Only those members of the research team whose role requires access to personal identifiers will have access. The clinical samples are processed by registered healthcare scientists and are afforded the stringent information governance as given to all clinical samples processed by the Exeter Clinical Laboratories.

All paper copies of study data will be stored under ID number and kept in locked, access-controlled offices within the research facilities; research data will be held separately to identifiable information. Researchers involved in data analysis will not have access to personal identifiable data, only the

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anonymised research data. No identifiable data will be included in research publications or progress reports.

Any participant information required to be sent to a third party will adhere to these pseudo-anonymised parameters. No participant identifiable data will be sent outside the UK.

Anonymised clinical study data may be shared on a funder and sponsor approved participant-level data repository, if appropriate.

9.7 Indemnity

The lead Sponsor, University of Exeter, provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research participant for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions). Public liability insurance is provided to cover the design and management of the study.

NHS indemnity covers potential legal liability for harm to participants arising from the design of the research.

NHS indemnity covers potential legal liability of investigators/research staff for harm to participants arising from the conduct of the research.

9.8 Access to the Final Study Dataset and Archiving

During research, all records are the responsibility of the Chief Investigator / Principal Investigator and must be kept in secure conditions.

Personal data will be stored where consent is given by the participant and/or parent/guardian to be contacted for follow-up on their future health status, and/or about participating in future studies.

Where consent is given by the participant/parent/guardian, their remaining samples and data from the project will be gifted to the Genetic Beta Cell Research Bank (GBCRB), an approved tissue bank (REC ref: Wales Research Ethics Committee 5, 22/WA/0268) in Exeter to be used for future research. The GBCRB is managed by The Royal Devon University Healthcare NHS Foundation Trust's Exeter Genomics Laboratory. Access to samples/data is through application to the Genetic Beta Cell Research Bank steering committee.

When the research study is complete, it is a requirement of the UK Policy Framework for Health & Social Care and Sponsor Trust Policy that the records are kept for a further 15 years. At the end of the study, the study data will be archived by the CI at the University of Exeter.

10 DISSEMINATION POLICY

Results will be written up and submitted for publication in (open-access) peer-reviewed journal(s), and prior to open access preprint servers (e.g., such as medRxiv or bioRxiv). Abstracts will be submitted to national and international conferences. Results will also be presented to colleagues (clinical and research) at regular in-house meetings. Ongoing updates on study progress will also be made to Exeter PPIE group for continued feedback.

Some data will also be deposited in electronic archives that are available to other researchers upon request to ensure data is used only to advance scientific and medical understanding.

We will follow the funders' dissemination policies accordingly, such as regular meetings/interim report to update on progress of the research.

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Written information in the form of a letter/newsletter outlining the key findings of the study will be sent to all participants and uploaded to the Exeter CRF and study websites. It may be possible to organize an online event to present the study findings to interested participants.

Anonymised clinical study data may be shared on a funder and sponsor approved participant-level data repository, if appropriate.

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12 APPENDICES

12.1 Appendix 1 – Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
REC Responses	2.0	01 May 2024	A T Hattersley M Hudson	Updates made to protocol in response to REC queries.

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12.2 Appendix 2 – Required documentation

Study Documents

- Signed protocol and any subsequent amendments
- Sponsor Monitoring Plan and subsequent reports
- Data Management Plan
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from Sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics/HRA submissions/approvals/correspondence
- CVs of CI/PI and site staff
- UK regulations (GCP) course certificate of CI/PI
- Delegation Log
- Staff Training Log
- Recruitment Log
- Monitoring Visit Log
- Breach of Protocol Log
- Case Report Forms (Data Collection Forms)
- Correspondence relating to the study

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12.3 Appendix 3 – Research blood sample volumes

A: WHO Guidelines for research blood sample volumes

Table 1: WHO Guidelines for research blood samples in infants

Child's weight (kg)	WHO blood sample (ml) (0.75 ml/kg)	WHO Max blood sample (ml) (3.25 ml/kg)	ENDURE study visit MAX Sample Volume (ml)
10	7.5	32.5	15
12.5	9.3	40.6	19
15	11.3	48.8	23
17.5	13.1	56.9	28
20	15	65	28
22.5	16.9	73.1	33
25	18.8	81.3	33
27.5	20.6	89.4	38
30	22.5	97.5	43
32.5	24.4	105.6	48
35	26.3	113.8	48
37.5	28.1	121.9	53
40	30	130	58

Table 2: Maximum amount of blood collection for research per blood collection per age, according to WHO-guidelines'

Age group	WHO Max blood sample (ml)	ENDURE study visit MAX Sample Volume (ml)
Children aged 6 - 10 years	40	36
Children aged 10 - 15 years	50	44
Adults aged 16 and 17 years	60	54
Adults aged 18 and above	-	100

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12.4 Appendix 4 – Study flowcharts

ENDURE Core Study Flowchart (included in Core Study Information leaflet)		
ENDURE **Understanding beta cell disorders through the study of rare genotypes**		**Study:** **CORE**
What will happen during my research appointment?		
	What does this involve?	**Are there any risks?**
Arrive at Clinical Research Facility or chosen location **Give consent to participate** **15 -20 mins**	At the time of making your appointment, you will be asked if you require a parking permit. At your visit, a member of the study research team will discuss all aspects of the study with you. You will have the opportunity to ask questions and when you are happy that you understand what is involved, you will be asked to complete a form giving your consent to participate in the study.	No. Participation is entirely voluntary, and it is up to you whether to join the study and you can withdraw at any time without giving a reason.
Body measurements, medical history **20-25 mins**	You will be asked some questions about your general health and any treatments, plus family history of diabetes. We will measure and record your height and weight.	No.
Blood collection **10-15 mins**	We will insert a small cannula (thin plastic tube) into your arm to make the collection of blood samples more comfortable. The blood sampling will involve a single draw of blood. The exact number of blood samples vary for different individuals so will be explained in advance. The total amount of blood we will collect during the visit will follow WHO guidelines which factor for age and weight. *[Examples:* A 6-10 y child's sample will not exceed 36 millilitres (ml) (approx 2 tbsp). An 11-15 y child's sample will not exceed 44 millilitres (ml) (approx 2½ tbsp). A 16-17 y adult's sample will not exceed 54 millilitres (ml) (approx 3 tbsp) An adult's sample will not exceed 100 millilitres (ml) (approx 5½ tbsp).] The blood will be analysed to assess how genetic variants affect function and features of cells in the body. Immune system, genetic and insulin markers will be measured.	Blood sampling can cause some discomfort when the needle is placed in the vein to draw blood. There is also a possibility that a small bruise may develop. These risks will be minimised by the procedures being carried out by a qualified nurse/researcher who will monitor you closely throughout the whole procedure.
A member of the research team will make sure that you are comfortable before you leave the research facility.		

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ENDURE Imaging Sub-Study Flowchart (for inclusion with Core Study Information Leaflet)	
ENDURE **Understanding beta cell disorders through the study of rare genotypes**	**Sub-Study:** **Imaging**
You are eligible to take part in the Imaging Sub-Study, which involves you having an MRI (Magnetic Resonance Imaging) scan. If preferred, the MRI scan can be arranged as a separate visit to the Core Study visit. Please read the ENDURE Core Study information leaflet **and** the information overleaf. This will provide information about the MRI to help you decide whether you want to take part in the Imaging Sub-Study.	
What will happen during my research appointment?	
The research visit will take place at the NIHR Exeter Clinical Research Facility and the Mireille Gillings Neuroimaging Centre (MGNC), which are both located at the Royal Devon and Exeter Hospital in Exeter, England.	
What does this involve?	**Are there any risks?**
Arrive at Clinical Research Facility. **Give consent to participate.** **15-20 mins**	At your visit, a member of the ENDURE research team will discuss all aspects of the Imaging Sub-Study with you. You will have the opportunity to ask questions and when you are happy that you understand what is involved, you will be asked to complete a form giving your consent to participate in the Imaging Sub-Study.	No. Participation is entirely voluntary, and it is up to you whether to join the study and you can withdraw at any time without giving a reason.
Magnetic Resonance Imaging (MRI) scan **up to 60 mins**	For your MRI scan at, you will be asked to change into a gown provided and lie still in an MRI machine (a cylindrical tube/tunnel) for up to a **maximum** of 60 minutes. You can ask for breaks when and if required. This is a routine, safe, NHS procedure for which details can be found here: www.nhs.uk/conditions/mri-scan/ We will focus on taking images of your body to measure organ size and look at fat distribution.	Please read the information overleaf. Prior to making your MRI appointment, you will be asked to complete an MRI Safety Checklist Screening Form to assess your safety in the magnetic environment. A qualified researcher will monitor you closely throughout the whole MRI scan.
A member of the research team will make sure that you are comfortable before you leave the research facility.	

Please refer to Imaging Flowchart for additional information and consent statements.

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12.5 Appendix 5 – Glossary of terms and abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form / Clinical Research Facility
CRN	Clinical Research Network
DM	Diabetes mellitus
DMP	Data Management Plan
ECRF	Exeter Clinical Research Facility
GCP	Good Clinical Practice
HI	Hyperinsulinism
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
NDM	Neonatal Diabetes
Non-CTIMP	Non-Clinical Trial of Investigational Medicinal Product
OGTT	Oral Glucose Tolerance Test
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
R&D	Research and Development Office
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIV	Site Initiation Visit
SDV	Source Document Verification
SOP	Standard Operating Procedure
SMG	Study Management Group
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCR	T Cell Receptor
TMF	Trial Master File
T1D	Type 1 Diabetes