UKHR

United Kingdom Histiocytosis Registry

A Research Tissue Bank and Database to enable research on histiocytic disorders

Short Title: UKHR

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Signature page

UKHR Research Tissue Bank Protocol V2.0 4-Mar-2022

This protocol has been approved by:

Name: Professor Matthew Collin Trial Role: Chief Investigator

Signature: Date:

25.3.22

Amendments

Number	Date	Protocol version	Summary
1	22-Jan-2022	1.4	1. Addition of e-consent 2. Addition of consultative consent 3. Addition of Deputy CI 4. Revision of Local Investigators 5. Revision to format of protocol

Definitions

UKHR
United Kingdom Histiocytosis Registry: A Research Tissue Bank with Research Database clinical annotation

Chief investigator (CI)
Named investigator with responsibility for the conduct of Registry

Deputy Chief Investigator (DCI)
Named investigator with responsibility for the conduct of Registry

Co-Investigator (Co-I)
Named investigator with oversight for the Registry

Local Investigator
Named investigator at data/sample collection centre

UKHR Access Committee
Committee responsible for reviewing use of UKHR resources consisting of PI, Co-I, Local investigators, scientific and patient representatives

Personal Identifiable Information
Information relating to an individual including name, gender, ethnicity, initials, data of birth, year of birth, hospital number, address

Anonymised
Information that does not have any other personal information from which the identity of a participant can be deduced such as their name, date of birth, hospital number or address. Anonymised information may contain some personal information such as the year of birth, gender, ethnicity and country of residence.

Link-anonymised
Data that maybe linked to personal identifiable information, even outside a database. The Registry is link-anonymised. The link between the Registry ID and personal identifiable information will be maintained outside the Registry by the medical teams of the participants, for the purpose of collecting follow up and outcome clinical data.

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1. Background

Histiocytic disorders are rare and potentially life-threatening illnesses that are well-recognised in children but can occur at any age.

Haemophagocytic Lympho-Histiocytosis (HLH) is an immune system disorder characterised by abnormal macrophage activation owing to a genetic defect in the immune response to viruses. It is associated with great than 50% mortality and may require urgent hematopoietic stem cell transplantation to achieve durable remission. A genetic aetiology is defined in up to two-thirds of paediatric patients[1] but many questions remain concerning the aetiology in adults and optimal management [2–5].

Histiocytic Neoplasms are rare diseases characterized by an accumulation of mononuclear phagocytes, infiltrating the skin, bones, lungs, liver, spleen, bone marrow and central nervous system[6–8]. They are are caused by somatic mutation in MAP kinase pathway genes, leading to the prolonged activation and survival of tissue dendritic cells and macrophages[9–11]. Histiocytic neoplasms are diverse. The most common entities are Langherhans cell histiocytosis, Erdheim Chester Disease, Rosai Dorfman Disease and various forms of Xanthogranuloma. A number of related disorders with prominent populations of histiocytes also exist, for which the aetiology remains unknown.

Clinical presentation of histiocytic neoplasms is very diverse, ranging from innocent skin nodules to life-threatening malignant inflammatory disease. A recent reclassification has been proposed based on site and histology[12]. About half of histiocytic disorders are caused by a point mutation creating a constitutively activated RAF protein, BRAFV600E. The remainder involve mutations of RAS, MEK and other members of the MAPkinase pathway. Genotyping lesions with DNA sequencing has huge potential to assist in the diagnosis of histiocytosis, although this has not yet been routinely applied in the UK[10,13].

Histiocytic neoplasms affect all ages with an estimated annual incidence of 1 per million., higher in children. Although rare, the incidence is approximately equivalent to that of acute myeloid leukaemia or lymphoma in children[8]. Children are cared for in the UK by a network of paediatric oncologists, although there is no formal service specification in the NHS. Adult patient services are fragmented across several specialities and the true incidence and prevalence are more difficult to assess[14]. In order to meet the challenges of adequate service provision, more information is required about the incidence and prevalence of histiocytosis and the healthcare burden incurred, in all ages.

Treatment of histiocytic neoplasms in children has evolved through a number of international trials LCH I to IV[15]. These have primarily used conventional approaches with corticosteroids and chemotherapy. In adults there are no randomised treatment trials of any kind. The discovery of MAP kinase pathway mutations has suddenly opened up the prospect of treating difficult patients with targeted drugs such as BRAF and MEK inhibitors, highly developed for use in melanoma. However, genotyping is not routinely performed and therefore many questions remain unanswered about the appropriate use of targeted therapy[10,13].

Many of the pressing questions in the diagnosis and management of patients with histiocytosis can begin to be answered by creation of a UK Histiocytosis Registry (UKHR). The essential demographics of histiocytosis in the UK are not well documented, impeding the provision of service and recruitment to clinical trials. Much work also needs to be done to bring DNA sequencing to frontline pathology diagnosis, to understand the value of genotyping histiocytic lesions and to develop clinical trials and protocols for access of targeted therapies. Children recruited to LCHIV have access to a CRUK-funded biology study that provides lesion genotyping and some level of molecular monitoring. However, provision of services for those not on trial or for adults remains inconsistent.

In addition to UK-based clinical and basic research activities, a number of organisations outside the UK have proposed international registries for histiocytosis. Another motive for creating the UKHR is to act as an interface with these international registries. These include: International Rare Histiocytic Disorders Registry (IRHDR; Toronto), Histiocytic Disorders Registry (HDR; Vienna) and Erdheim Chester Disease Global Alliance Registry (ECDGAR; New York). In order for UK patients to participate in these registries, specific consent will be sought for sending their anonymised clinical data overseas. In the cases of rare histiocytosis, histiocytosis in adults and ECD, it is essential that the UK join international efforts to explore the epidemiology, natural history and health economics of these disorders.

The UKHR will recruit participants with any histiocytic disorder including:

A. Haemophagocytic Lympho-Histiocytosis (HLH)

B. Histiocytic neoplasms
- Langerhans cell histiocytosis (LCH)
- Erdheim-Chester Disease (ECD)
- Rosai-Dorfman Disease (RDD)
- Juvenile xanthogranuloma (JXG)
- Xanthoma disseminatum (XD)
- Various cutaneous histiocytosis disorders
- Malignant histiocytosis

C. Related histiocytic disorders including
- IgG4-related disease
- Sarcoidosis
- Granulomatous diseases
- Giant cell diseases
- Vasculitis

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2. Aims and objectives

The aims of UKHR are as follows:
- Establish a cohort of well-characterized histiocytosis patients to facilitate epidemiological, natural history and health economic studies.
- Provide information about the incidence, demography and healthcare burden of

histiocytosis to facilitate planning, commissioning and resource allocation.
- Learn more about the value of genotyping in disease subtypes, risk factors, response to therapy and personalised medicine
- Promote more consistent diagnoses, develop guidelines for best practice, and facilitate entry into trials
- Encourage collaborative research nationally and internationally on histiocytosis.

The UKHR was designed as Research Tissue Bank.

Link-anonymised clinical information will be collected in order to annotate studies using collected tissue but also to provide sufficient detail for comprehensive demographic, clinical and healthcare burden studies to be conducted.

As a Research Tissue Bank, The UKHR will be permitted to obtain an extra sample of fresh blood up to 60ml or 3 tablespoons (for adults, age-appropriate for younger participants), fresh biopsy tissue and to collect archival tissue from NHS pathology laboratories. The extra fresh blood samples will be additional to those required for routine clinical care but taken during the same venepuncture. The collection of fresh tissue is important for a number of biological and molecular studies that are not possible using fixed tissue.

3. The UK Histiocytosis Registry

3.1 Access Committee

An Access Committee, consisting of the Investigators, a scientist with knowledge of histiocytes and at least one patient representative, is responsible for reviewing and approving applications from research organisations for the use of samples and clinical data from the UKHR. The investigators are permanent members of the Access Committee, and the term of the membership for the remaining members is 5 years, renewable for an additional term.

3.2 Clinical data and samples management

The Chief Investigator and Deputy Chief Investigator are responsible for publicising the UKHR, as well as co-ordination of clinical data and samples collection, and monitoring of recruitment centres, currently supported by a departmental data manager.

The Project Manager assists in data entry, maintaining an accurate and up-to-date record of the data collected and any data analysis, resolves any data discrepancy, and maintains the quality standard of the data collected for the UKHR, keeping an audit trail of the clinical data released to other researchers.

The Person Designate is responsible for sample processing, storage and the maintenance of an up-to-date record of the samples stored as well as an audit trail of the samples released to other researchers.

3.3. Recruitment centres

Specialists providing secondary care for patients with histiocytosis are invited to join as Co-Investigators and will serve as Local Investigators for the recruitment of patients as outlined in the Registry Personnel. The annual report to the Ethics Committee will contain details of active sites and recruitment. At each recruitment centre, a senior clinician (usually a consultant with an interest in histiocytosis) will be the named Local Investigator, who will be responsible for coordinating patient recruitment and transfer of data and samples to the UKHR, maintaining the anonymity of data transferred to UKHR using the Registry ID codes and ensuring compliance of data confidentiality and security. Additional centres with may be added following approval of the Access Committee.

4. Database software and website development

4.1 UKHR database

The UKHR database will hold no personal identifiable information except year of birth, gender and ethnicity. A secure website for input of data to the registry will be developed by the database manager using REDCap software (https://www.project-REDCap.org/), via Newcastle University's REDCap service. Data will be stored in Newcastle University's secure REDCap server. For details of the fields held in the database (see document**: *UKHR Registry Elements*).**

4.2 Local NHS Databases containing links to identifiable data

Local Caldicott-approved NHS databases containing details of participants recruited at each local site including the links to the UKHR Registry ID number will be kept by medical teams at their sites. In common with other clinical information required by the medical team, these will be hosted on secured NHS servers on a restricted-access drives behind a firewall, preventing unauthorised access. The database manager has developed a simple database using a Microsoft Access template that can be used locally for this purpose. The link between Registry ID codes should be maintained by an individual with an NHS contract not directly involved in the research. The Local investigator will be responsible for appointing such an individual. The Local Investigator should not take this role themselves as they are directly involved in the research.

5. Clinical governance, sponsorship and funding support

5.1 Research sponsorship

The Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) is the sponsor of the study.

5.2 Data and sample collection and transfer between centres

Data will be added by Local Investigators or appropriately trained delegates directly to the database using a remote connection to the REDCap server hosted by Newcastle University. Where FFPE tissue is required for specific research projects, archival samples will be retrieved from local pathology laboratories, de-identified and relabelled with only the UKHR ID number. Fresh biopsy samples and blood will be, identified only by the UKHR ID number and transported directly for storage in the Newcastle Biobank. Transfer of digital imaging where required, will also be identified only by the UKHR ID number. Standard operating procedures will be developed for data and sample collection and transfer. A service level agreement will be made between all recruitment centres and Newcastle University to describe the responsibility of the collection centres and Newcastle University. For the purpose of data verification, Local Investigators will be able to review their own participant data and the PI and database manager will have overview of all entered data.

5.3 Sample storage

The HTA license number is 12534, held by Newcastle University, valid from 06 July 2016
The Licensed Premises is:

Newcastle University
Framlington Place
Newcastle Upon Tyne
NE2 4HH

The Designated Individual is:

Dr Christopher Morris

Translational and Clinical Research Institute
Newcastle University
c.m.morris@newcastle.ac.uk

5.4 Funding

UKHR database infrastructure has been funded by a grant from Histiocytosis UK to pay for the Database Manager, Project Manager and NHS costs of sample retrieval from NHA pathology archives. A biomarker project from CRUK also contributes to molecular testing of blood and fresh biopsy samples.

The study will also be registered to the UK Clinical Research Collaboration (UKCRC) Tissue Directory and Coordination Centre. Initial funding has been provided by Histio UK, which has been granted NIHR non-commercial partner status. An application will also be made for adoption as a rare disease to the NIHR Bioresource, which attracts further resources for biobanking and analysis.

6. Recruitment procedures and eligibility criteria

6.1 Study enrolment

Research participants will be enrolled at Newcastle upon Tyne Hospitals NHS Foundation Trust and nominated collection centres where Local Investigators affiliated to the registry will be responsible for identifying and approaching potential participants.

Research participants may also be identified through National Advisory Panels / MDT meetings dealing with HLH and histiocytic neoplasms. Members of the clinical care team attend these meetings and will be asked to approach their patients for consent.

6.2 Identification of participants

The CI or Co-I / Local Investigator will approach potential participants during their routine clinic appointments and inpatient duties. In collection centres where there are pre-existing databases of histiocytosis subjects, the Co-I / Local Investigator may send potential participants an invitation and written information prior to their clinic appointments using the standard invitation letter (see documents: ***Letter of Invitation Adult, Letter of Invitation Parent and Reply Slip***). All participants will be given written information and sufficient time to ask questions concerning the project.

Participants in a critical care setting may lack capacity owing to delirium, sedation or medical intervention (for example intubation). They will be approached through a consultative consent process involving their Personal Consultee, Next of Kin, or Welfare Attorney. If this is not possible then a Registered Medical Practitioner unrelated to the Research Tissue Bank will be approached to act as a Nominated Consultee.

7. Consent and sample/data collection procedures

Evaluable research participants are defined as those who consent for collection of their clinical data, including review of digitised pathology and imaging where required, and give permission for archival pathology samples or fresh blood and biopsy samples to be collected and used for research.

The collection of fresh biopsy tissue will include some participants whose diagnosis is not yet confirmed since the collection of fresh tissue is usually only possible at initial diagnosis.

The consent procedure used will be that employed for tissue banking that is stored for research use in compliance with the Human Tissue Act. Written or electronic consents will be obtained before any study procedures are performed. The general procedure for obtaining informed consent in compliance with the HTA is described in ***Appendix 1***.

7.1 Consent procedure:

- Participant or parent/guardian is provided with information and consent/assent forms by the Local Investigator or from the UKHR website (www.UKHR.org), or electronically via XXX.
- The Local Investigator will review consent forms in person or by telephone or video call with participants or parents/guardians and will obtain their consent.
- In the case of participants from other Institutions outside the data/sample collection centres, consent can be obtained with the help of a local delegate or electronically via XXX.
- Participants in a critical care setting who lack capacity, owing to delirium, sedation or medical intervention (for example intubation) will be approached through a consultative consent process involving their Personal Consultee, Nearest Relative, or Independent Mental Capacity Advocate (IMCA). If this is not possible then a member of the clinical care team unrelated to the Research Tissue Bank will be approached to act as a Nominated Consultee. The approach to potential consultees is described in more detail in Section 7.2 below
- In the case of non-English-speaking participants, consent can be obtained with the help of a local approved hospital translator.
- The Local Investigator will contact UKHR to obtain a unique study identifier for the participant and write it on the consent form. This will be stored locally and used by the medical team to link the participant with the link-anonymised data sent to the registry. In the case of electronic consent, the unique identifier will be held by the REDCap database.
- The Local Investigator will submit signed consent forms to the UKHR via secure NHS email or the consent will be captured electronically.
- Details of any consent opt-outs will be recorded on the Registry database

7.2 Approach to potential consultees for patients who lack capacity

The Principal Investigator or Co-Investigator at will ask a member of the clinical care team to approach the patient's Nearest Relative in order to identify a potential Personal Consultee, likely to include the Nearest Relative. In the absence of a Nearest Relative, the Principal Investigator or Co-Investigator may ask the clinical care team if there is a member of the team willing and able to act as a Nominated Consultee. If the patient has no Nearest Relative, then this discussion will also involve the Independent Mental Capacity Advocate (IMCA) appointed for the patient. Any member of the clinical care team who knows the patient and is trained in assessment of patients who lack capacity may act as their Nominated Consultee including a doctor, senior nurse or IMCA.

7.3 Electronic consent

SOPs concerning the use of electronic consent in research at Newcastle unpon Tyne Hospitals (NJRO-GEN-SOP-028) and the use of REDCap for this purpose (NJRO-INF-SOP-003) are included as ***Appendices 3 and 4***.

Participants who wish to provide consent electronically will be contacted by telephone initially and provided with electronic or hard copy version of the relevant Information Sheets. A video

call will be set up to confirm their identity and to conduct an interview to answer questions and to confirm that their consent to join is informed. The process will adhere to the SOP developed by the Newcastle Joint Research Office for use of their REDCap database (Appendix 4). In summary the prospective participant will use 'Survey login' to confirm their identify and access electronic versions of the Information Sheets and Consent Forms constructed by the NJRO Informatics Team.

7.4 Ongoing consent:

Ongoing consent will be confirmed in line with good clinical practice. Adults who were included while incapacitated will be re-consented when they gain capacity. For children, separate patient information sheets have been created for 0-6, 6-10 and 10-15 year olds. These will be used as appropriate as young participants grow up, in conjunction with the child assent form. At 16, participants will be re-consented using the adult information sheet and consent form.

7.5 Data collection:

- Data will be entered directly onto the registry database by the Local Investigator or their delegate using REDCap using the Local Investigator's username and password which will be supplied by the registry team
- The PI and Data Manager will check the data. Any missing or outlying data will be validated with the Local Investigator.
- Data required by International Registries will be transferred through the REDCap system.
- Pathology slides, reports and images will be link-anonymised prior to transfer to International Registries

7.6 Sample collection:

FFPE sections. Sections of histiocytic lesions will be requested from NHS pathology lab archives for specific projects such as central review of pathology and development of new diagnostic tools including immunohistochemistry and nucleic acid sequencing. Although this material will not actually be stored by the Registry, HTA regulations require that material will be logged to the Registry under the Registry ID number and signed out to the specific project. **Fresh blood and tissue**. The UKHR will be permitted to obtain an extra sample of fresh blood up to 60ml or 3 tablespoons (for adults, age-appropriate for younger participants). Samples will be transferred for physical storage to the Research Tissue Bank held at Newcastle University under HTA license. Alternatively samples may be held in local HTA approved Research Tissue Banks and transferred under Biobank to Biobank protocols.

8. Anonymisation, confidentiality, data security and personal identifiable data

8.1 Anonymisation procedures and confidentiality

All clinical data and samples collected by UKHR are held link-anonymised with minimal personal identifiable information: year of birth, gender, ethnicity and residence in the UK. The UKHR Registry ID will be used to communicate with Local Investigators at data and tissue collection centres and for transfer of information to International Registries. Laboratory research notebooks will contain only with the UKHR Registry ID. The key linking the UKHR Registry ID with donor identity will only be held by a member of the medical team with an NHS contract and will be kept in secure physical or electronic locations in the NHS domain. Electronic consent will be held in the REDCap database which is compliant in data security standards required for identifiable information. Details of the link-anonymisation procedure to be used are given in ***Appendix 2***.

8.2 Data security

Access to the entire registry data set will be restricted to the Chief Investigator, Deputy CI and approved individuals who have submitted data requests approved by the Access Committee. Co-I / Local Investigators will have access to participants from their own institutions to allow data checking and addition of prospective clinical data. All accesses and changes to the database will be logged and audited. The data on the database will be backed-up according to Newcastle University's REDCap service policy.

9. Patient criteria

9.1 Inclusion criteria

- Any age at diagnosis.
- Diagnosis of histiocytosis or related disorder, established before or after the opening of the registry.
- Cases diagnosed from 1st January 1995 until the present time and prospectively.
- Signed informed consent by a patient, parent/guardian, or consultee
- Deceased patients can be included provided that the legal representative is contacted at least 6 months after the death of their relative and not on the birthday or anniversary of death of the relative.

9.2 Exclusion criteria

- Informed consent has not been signed.
- Cases diagnosed before the year 1995.

10. Submission of data and pathology samples to partner international registries

Selected data will be supplied to International Registries. Data will be link-anonymised but will include year of birth, gender, ethnicity and residence in the UK. These demographics are required for epidemiological clinical research. Each participant will be assigned a separate identifier for each registry to which they agree to submit data, and these identifiers will be stored on the UKHR and used in all correspondence with the other registries.
Current partner registries are:

- The International Rare Histiocytic Disorders Registry (IRHDR) based in Toronto, Canada.
- The Registry for Histiocytic Disorders (RHD) based in Vienna, Austria.
- The Erdheim-Chester Disease Global Alliance Registry (ECDGAR) based in New York, USA.

If another national/international histiocytosis registry is created, a protocol amendment will be submitted for ethical approval to allow the UKHR to provide relevant data to it.

10.1 IRHDR

The International Rare Histiocytic Disorders Registry (IRHDR, https://clinicaltrials.gov/ct2/show/record/NCT02285582) is for participants with non-Langerhans cell histiocytosis based at the Hospital for Sick Children in Toronto, under the leadership of Dr Oussama Abla and the funded by the Histiocyte Society, using REDCap software. In addition to clinical data, the IRHDR requires central pathology review to make sure that these rare disorders are consistently diagnosed. Participants with a rare histiocytosis will be shown additional information about this registry (see document ***Supplementary Information for IRHDR***), and asked if they are willing to provide data to the IRHDR, and samples for pathology review. UKHR will submit link-anonymised data to the IRHDR using a REDCap secure online website

similar to the UKHR's own REDCap website. The data is stored on a secure server at the SickKids research data centre (see document ***Supplementary Information for IRHDR*** for details).

10.2 Central pathology review

This review is not intended for clinical care but only for integrity of the database. Samples will by checked for completeness and suitability by the Principal or Local Investigator and sent by NHS-approved courier from the submitting centre direct to the central review pathologist:

Ivo Leuschner, MD, PhD,
Kiel Paediatric Tumor Registry,
Dept. of Paediatric Pathology,
University of Kiel, Germany

Cases will be deemed "acceptable" or "not acceptable for inclusion" by the pathology reviewer. Information from UKHR required to accompany the pathology sample is outlined in the IRHDR protocol and includes local pathology report and summary clinical information which will be provided in anonymous format using the UKHR and IRHDR registry ID numbers. Either the tissue block or 1 H&E and 10 unstained slides for immunostains are required and will be returned to the originating pathology laboratory after review

10.3 Clinical issues related to pathology review

In the event that the pathology review reports a difference compared with the initial diagnosis, the IRHDR will inform the UKHR and the PI will notify the medical team of the participant. Since there are no standards of care for rare histiocytic disorders, owing to their small numbers, this is unlikely to impact upon patient care. Any unforeseen circumstances in which there is a therapeutic implication through a change in diagnosis, the case will be discussed by international experts in histiocytosis who advise the IRHDR, in order to give the best advice to the medical team.

10.4 RHD

The RHD is for adults with any type of histiocytosis under the leadership of Dr. Michael Girschikofsky at the Elisabethinen Hospital, Vienna, funded by the Histiocyte Society. Adult participants will be shown additional information about this registry (see document: ***Supplementary Information for RHD***), and asked if they are willing to provide data to the RHD. UKHR will submit link-anonymised data using a secure online website created specifically for the RHD. The data is stored on a secure server by IT company T-Systems Austria (see document: ***Supplementary Information for RHD***, for details).

10.5 ECDGAR

The Erdheim-Chester Disease Global Alliance Registry (ECDGAR) is for participants with Erdheim-Chester Disease (ECD) and is led by Dr Eli Diamond at the Memorial Sloan Kettering Cancer Center in New York, USA using the REDCap system.
Patients with ECD will be shown additional information about this registry (see document: ***Supplementary Information for ECDGAR***), and asked if they are willing to provide data including link-anonymised digital images of their radiology to ECDGAR. The UKHR will submit link-anonymised data for participants with ECD to the registry using a REDCap secure online website (see document: ***Supplementary Information for ECDGAR***, for details).

11. Access to clinical data and samples

The UKHR Access Committee will control access to the information and samples held in the registry. Research proposals on histiocytosis or related disorders will be considered from academic researchers and their industrial collaborating partners from within the UK and outside the UK.

11.1 Application

All researchers requesting the use of the UKHR data and/or samples must apply to the UKHR Access Committee using a standardised application form (see document: ***UKHR Application for Data or Samples***). The following criteria will be used to assess the research proposals:

1. Scientific merits of the proposed research
2. Whether the proposed study addresses an unmet need in histiocytosis research and treatment
3. Whether the proposed research falls within the remits of the objectives of the UKHR

All applications will be considered using the same criteria regardless of the types and locations of the research organisations. Formal approvals will only be granted after the Access Committee has received evidence of sufficient funding support for the proposed research, research sponsorship and approvals from relevant regulatory bodies locally (if applicable).

11.2 Types of research considered

Data and samples from participants will only be used for research directly on histiocytosis and related conditions. Possible research projects will include a wide range of laboratory and hospital-based research. For example: to find out what causes histiocytosis, to develop better tests to diagnose and predict the severity of histiocytosis, and to develop better treatment. The database may also be used to identify suitable individuals with histiocytosis for future research and clinical trials.

We will ask participants for specific consent for their samples/data to be included in studies using the following research methods:

1) DNA and RNA sequencing include part or even all of the genome to understand what genes have caused histiocytosis. This will include germline variants in the case of HLH and somatic mutation in the case of LCH and other 'neoplastic' histiocytoses.

It is clearly stated in the PIS that the research will only study genes that are likely to be associated with histiocytosis. The research will not look for genes that are associated with other diseases and participants will not receive information about the genetic risk of diseases that are not related to histiocytosis.

It is also stated that it is possible that genes that cause histiocytosis might also be associated with other illnesses. However, this type of knowledge is continually advancing all the time and we cannot predict the chance that a histiocytosis gene will be linked to another illness, to participants.

Current guidance on the genes that may be associated with HLH may be found in a regularly updated publication from the International Union of Immunological Societies (IUIS) PID expert committee:
Bousfiha A, Jeddane L, Picard C et al. The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. *J Clin Immunol*. 2018;38 (1):129-143.

Guidance on the genes that may be subject to somatic mutation in LCH-type histiocytosis potentially include all genes listed in the catalogue of somatic mutations in cancer (COSMIC). This is regularly updated and may be found at: https://cancer.sanger.ac.uk/cosmic

2) making 'immortal' cell lines (i.e. growing cells from biopsy or blood samples in the laboratory so that they can survive for a long time outside the body), including 'stem cells', to preserve a supply of material
3) growing histiocytosis in mice to study the effect of histiocytosis on different organs

A list of all the research studies using the information/samples of the UKHR will be published on our website (www.UKHR.org.uk).

11.4 Data/samples released to other researchers

- No data or sample will be released to any researcher without a formal approval from the Access Committee.
- All data/samples will be released in a link-anonymised format to the researchers.
- A Material Transfer Agreement will be arranged between the UKHR and the receiving organizations to ensure that:
    - clinical data and/or samples released to the researchers will be used solely for the specific study approved by the Access Committee;
    - clinical data and/or samples will not be transferred to other researcher(s) without formal approval by the Access Committee;
    - the researcher will either return or destroy all unused data and/or samples upon completion of the study
    - the researcher will either return or destroy all unused data and/or samples if a participant withdraws their consent
    - The UKHR has the right to request a copy of the raw data generated by the researcher(s) using the clinical data/samples of the UKHR if the Access Committee considers such data will add value or enhance the utility of the UKHR biomedical resource.
- An up-to-date record of data and/or samples released to other researchers will be kept.
- The details of all research projects covered under this application will be reported to the Research Ethics Committee on an annual basis.
- The quantity of samples to be released to each researcher will ideally be based on pilot data. If no pilot data were available, then samples may be released in stages, so that the quantity of samples required for the entire project can be more accurately determined.
- All researchers using the clinical data/samples must submit a written report to the Access Committee within 6 months of the completion of the study. In addition, for research projects of 3 years or longer, an annual interim report on the progress of the project is required.

12. Procedures for dealing with incidental findings

If the participant has a rare form of non-Langerhans cell histiocytosis, and consent is obtained, their diagnosis will be checked by an expert for the IRHDR. If the diagnosis changes in a way that would influence the participant's treatment (or family of the participant, if the participant is deceased), then their care team will be informed.

No other incidental findings wil be communicated to participants or their medical teams. This includes genetic risk of unrelated diseases that is incidentally found by overlap with histiocytosis or that emerges as the result of future research, as outlined in section 5.2

13. Procedures for dealing with withdrawal of consents

13.1 Notification of UKHR

Investigators who receive requests for withdrawal from participants will inform the Data Manager of the UKHR as soon as possible, using the registry ID. Participants requesting withdrawal of consent will be asked whether their withdrawals relate to the use of their clinical data, samples and/or future contact for research studies and their responses will be recorded using the Withdrawal Form (see document: ***Withdrawal Form***). The participants will be asked to check and sign the completed Withdrawal Form to ensure that their requests have been

accurately documented. A copy of the signed Withdrawal Form should then be sent to the UKHR.

13.2 Disposal of clinical data/samples

If the participant requests, stored clinical data and samples at the UKHR will be disposed of according to the preference of the subject as soon as possible. The Principal Investigator will also contact all researchers who have received the clinical data or samples of the subject concerned and request that the clinical data/samples to be returned to the UKHR for disposal or be destroyed locally. Researchers are required to provide written confirmation that the data/samples have been destroyed accordingly.

14. Communications and publicity

We have created a website (www.UKHR.org) for the UKHR to contain information on the registry, including the recruitment centres and key contacts, the types of clinical data and samples that are being collected, progress on recruitment and the application procedures for use of clinical data and biobanked samples.
We will present the UKHR set up and summary data at scientific meetings and in peer-reviewed journals.

Appendix 1: Consent procedures in compliance with Human Tissue Act 2004

Background
As defined in the Human Tissue Act (2004), human tissue may only be used for research if patients or volunteers have given specific consent for their tissue to be used in an individual study or general consent for their tissue to be stored for potential research use. "Tissue" in this context includes cells, tissue biopsy specimens, larger tissue resections, whole organs and body parts. In all cases, research studies may only be undertaken following approval by a Research Ethics Committee or an equivalent procedure. We will be storing samples for this project that are regarded as "tissue" under the HTA. Consequently, it is necessary to have clear documentation of the nature of the consent that has been obtained in compliance with the HTA. Policy and procedures must also operate to ensure that human tissues, together with materials and information derived from them, are withdrawn from studies if patients withdraw consent retrospectively during the course of the project.

Procedure
1. The Principal Investigator (PI) will be responsible for maintaining records of consent for the project. The PI will be responsible for auditing these records on a regular basis, and for ensuring that appropriate action is taken if consent is withdrawn during the course of the project.
2. It will not generally be a requirement for the PI to hold copies of the original consent forms signed by participants but he/she will hold records to include:
(i) Written confirmation from originating source that consent has been obtained for all samples submitted
(ii) Specimen copy of consent form
(iii) Copy of relevant patient information leaflet(s)
3. The PI will ensure lines of communication and specimen tracking that will make it possible to return/dispose of any human tissue/biological specimen/clinical data (and any materials derived from it) if a participant withdraws his/her consent to their use during the course of research project. Data derived from such specimens must also be removed from the study
4. The PI will have a written procedure for the action to be followed in order to achieve return/disposal under such circumstances, and to ensure that derived materials/data are not used.
5. The PI will audit consent procedures on at least one occasion during the lifetime of each study involving human tissue and should include such audit results in the final report submitted on completion of the project. This should involve obtaining copies of a randomly or systematically selected set of consent forms or requesting specific confirmation of generic consent for all specimens from a selected hospital/institution.
6. The results of such audits must be communicated to the HTA Designated Individual for this registry, or his/her nominee.
7. The PI will ensure that all recruiting clinicians and institutions are notified and provided with new copies if consent forms or patient information leaflets are updated.
8. The PI must provide a report to the Designated Individual or his/her nominee of the action taken with regard to tissue samples, derived materials and data if consent is withdrawn by a participant during the course of the project. Such reports must be available for audit and be included in the final report submitted on completion of the project.
9. To comply with the Human Tissue Act 2004, the Designated Individual will audit consent annually, by requesting examples of the evidence described above.

Appendix 2: Anonymisation procedures: Human Tissue Act 2004

Background
The data held by UKHR is link-anonymised and does not contain any strongly identifiable personal information. It holds only the year of birth, gender, ethnicity and UK resident status. However, a link will be maintained securely between the unique study identifier and patient identifiable information outside the Registry by the medical teams of participants. This will allow prospective data to be gathered or patients to be re-contacted by the local medical team. Researchers who work with the information and samples will only see anonymous information, In accordance with the recommendations of the Research Ethics Committees and the Caldicott Guardian, the link is will be maintained by a member of the medical team with an NHS contract who is not directly involved in the research. The Local Investigator is directly involved in the research and so will be responsible for appointing another individual to maintain the link.

Scope
The Chief Investigator and the Co-investigators / Local Investigators at the tissue collection centres will be responsible for ensuring that samples are appropriately anonymised and for auditing these procedures for their groups on a regular basis. Anonymisation can only be performed by individuals who hold a substantive or honorary contract with a relevant NHS trust (i.e. the tissue collecting hospitals).

Procedure
All data and samples will be anonymised at source before they arrive at the UKHR.
A unique patient identifier will be obtained when the patient's data is entered onto the UK histiocytosis registry.
Samples will be labelled with the patient's unique identifier and the date and time of collection only. They will not contain any personal identifiable information.
Labels will be securely attached to the sample. Techniques will be used which ensure that legibility is preserved under the relevant storage conditions.
On receipt, samples will be inspected for labels containing personal information. Any personal information should be removed or obscured. Alternatively, if feasible, the sample may be transferred to a new receptacle which should then be labelled with the sample code and any other relevant information.

The key linking sample code with donor identity will be held only by an approved individual in the medical team with an NHS contract and will be kept in secure physical or electronic locations on NHS property. To comply with the Human Tissue Act (2004), the Newcastle University's Designated Individual for its license to store human tissue for research will audit sample anonymisation annually, by a process of laboratory inspection.

References
Human Tissue Act (2004) http://www.legislation.gov.uk/ukpga/2004/30/contents
Data Protection Act (1998) http://www.legislation.gov.uk/ukpga/1998/29/contents

Appendix 3: Virtual and e-consent in Research at NuTH

Newcastle Joint Research Office

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

Virtual and e-consent in Research at NuTH

NJRO-GEN-SOP-028

Newcastle Joint Research Office

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

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Newcastle Joint Research Office

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

1. Background/Introduction

Electronic methods for seeking, confirming and documenting informed consent (otherwise termed 'e-consent') are becoming increasingly popular in research, either to supplement the traditional paper based approach to consent, or where appropriate, replace it. Remote/virtual methods for seeking, confirming and documenting informed consent are also becoming more common. The Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA) have subsequently published a joint statement on seeking consent by electronic methods (September, 2018). Whilst the statement focuses primarily on clinical trials, the basic principles can be applied to all research conducted within the UK when consent is sought via electronic means.

Researchers however should be mindful that the use of e-consent may unintentionally discriminate against those who are not comfortable or who cannot use such technology (such as those who have a lack of familiarity with electronic systems, poor eyesight or impaired motor skills), therefore alternative methods for the provision of information and/or documentation of consent should be available for those who are unwilling to use electronic methods (HRA & MHRA Joint statement, 2018). There are however potential advantages of using e-consent systems, such as improving the informed consent experience by offering an interactive and engaging approach; rapid notification of amendments to participants that may impact their willingness to participate; and the promotion of timely e-consent data entry.

2. Purpose

The purpose of this SOP is to describe the methods and principles for seeking, confirming and documenting informed consent by electronic means (e-consent) at NuTH. Many principles within this SOP may also apply to remote/virtual consent.

Throughout this SOP, e-consent refers to the use of any electronic media such as text, graphics, audio, video and websites to convey information related to the study and to seek and/or document consent via electronic devices such as smartphones, tablets or computers.

3. Scope of Document

This SOP is applicable to researchers and support staff seeking, confirming and documenting e-consent/remote consent for studies sponsored and hosted at NuTH.

This SOP is also applicable to all NJRO staff that provide guidance and support on hosted research at NuTH.

This SOP is also applicable to all NJRO and trial management staff who work on NuTH sponsored research, where the CI wishes to utilise appropriate e-consent or virtual/remote consent methods (with agreement from sponsor) within their research.

4. Definitions

CTIMP: Clinical Trial of an Investigational Medicinal Product
e-consent: electronic consent
e-signature: electronic signature
HRA: Health Research Authority
ICF: Informed Consent Form
MHRA: Medicines and Healthcare products Regulatory Agency
NuTH: Newcastle upon Tyne Hospitals
PIS: Patient Information Sheet
RCT: Regulatory Compliance Team

5. Roles & Responsibilities

It is the responsibility of all research staff delegated the task of receiving consent to ensure they read and follow this SOP when utilising e-consent or virtual/remote consent methods.

It is the responsibility of NJRO sponsor representatives to ensure any e-consent/remote consent methods proposed in NuTH sponsored studies comply with this SOP, and that any methods are risk assessed (with risk mitigations proposed) where appropriate.

The RCT within the NJRO are responsible for overseeing the vendor assessment process for any third party providing e-consent services in NuTH sponsored high risk trials.

6. Procedures

6.1. Electronic Signatures

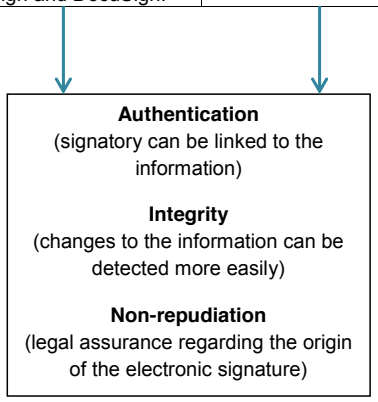
The UK eIDAS Regulations (SI 2016/969) defines an electronic signature as '*data in electronic form which is attached to or logically associated with other electronic data and which is used by the signatory to sign*'.

The MHRA GxP Data Integrity Guidelines and Definitions (Revision 1, March 2018) define an electronic signature as: '*A signature in digital form (bio-metric or non-biometric) that represents the signatory. This should be equivalent in legal terms to the handwritten signature of the signatory.'*

Electronic signatures may include tick box plus declarations; typewritten; scanned; electronic representation of a handwritten signature; unique representation of characters; digital representation of characteristics (e.g. fingerprint); and a signature created by cryptographic means. However, the type of electronic signature required for e-consenting in research varies depending upon the nature, complexity and risk of the trial.

Electronic signatures can be defined in to 3 groups:

Simple	Advanced	Qualified
E.g. stylus or finger drawn signature; typed name; tick box and declaration; unique representation of characters; fingerprint scan.	These are uniquely linked to the signatory, are capable of identifying the signatory, allow the signatory to retain control, and are linked to data within the signature that can detect any changes made. Examples include AdobeSign and DocuSign.	An advanced electronic signature, uniquely linked to the signatory, that is created by a qualified electronic signature creation device, and which is based on a qualified certificate for electronic signatures.



Some electronic signatures are more reliable and provide greater assurance than others. For instance qualified electronic signatures are automatically granted the legal effect of a handwritten signature with mutual recognition throughout EU (HRA & MHRA Joint statement, 2018).

The method of authentication of electronic signatures used in a study should be proportionate to the nature/complexity of the research; the risks, burdens and potential benefits; and the ethical issues at stake.

Key considerations in identifying an appropriate risk based and proportionate e-consent process will include: Does your recruitment and consent procedures mean that you can:

- Trust that the person who signed is who they say they are (i.e. ensuring that the signature is attributable to the individual)
- Trust that the consent form they signed hasn't been altered (i.e. ensuring that the act of 'signing' is recorded within the system so that it cannot be altered or manipulated without invalidating the signature or status of the entry)
- Trust when the signature was applied (i.e. ensuring the signature is date stamped)
- Trust the security of the electronic signature (i.e. ensuring that it can only be applied by the 'owner' of that signature).
- Adequately demonstrate that trust is justified if required e.g. during an inspection/audit (i.e. ensuring the record of the signature can be associated with the entry made and how this can be verified with a full audit trail).

When considering the implementation of electronic signatures, it is important to consider if any patient identifiable data would be stored or accessible outside the site and the security of this data.

Any methods of e-consent and electronic signatures must be approved by the sponsor and the REC/HRA. Regardless of whether paper-based or multimedia formats are used, the process of obtaining voluntary and informed consent must be upheld in accordance with the principles of GCP and all regulatory requirements.

6.2. Seeking e-consent/remote consent in CTIMPs

6.2.1. Provision of Information in CTIMPs

The methods used to inform and document the consent of participants in CTIMPs must comply with The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).

Participants must be provided with information on the nature, significance, implications and risks of the trial and the right to withdraw from the trial at any time. A contact for further information (such as the local principal investigator) must also be supplied.

Participants must be provided with information by interview with the investigator or a member of the investigating team. This enables potential participants to understand the nature, significance, implications and risks of the trial so they are able to make

an informed decision about whether or not to partake. Simply providing potential participants with this information (by paper or electronic means) would not be considered an interview; this requires an interactive process that enables participants to ask questions and receive answers from the investigating team.

The interview should be conducted in person where possible, or where justified (and approved by a REC), by electronic methods that allow two-way communication in real time. Whichever method is used, it is essential that confidentiality is maintained, the communication method is secure and the method has been approved by the sponsor, REC and NJRO.

Investigators should (where possible) align with local practice at sites for e-consultations when setting up an interview for e-consent/remote consent. For instance 'Attend Anywhere' is an online service which is utilised in routine practice for video call appointments at NuTH.

Whichever method is used, it should facilitate thorough and interactive communication that enables the potential participant to understand what participation would involve. It should also allow for the confirmation of the participant's identity, particularly where the interview and documentation of consent are carried out by electronic means at a distance.

In trials where face-to-face verification is not possible, for example where the trial is to be conducted entirely remotely, the participant's identity may be verified visually via a video link (and asking the patient to confirm their name and date of birth) or other means. It may also be possible to utilise general practices or other NHS sites local to the participant in order to verify their identity. Please note: the conduct of a CTIMP remotely would need to be approved by both the MHRA and a recognised REC.

Where the e-consent process takes place at a research site, verification of the participant's identity should be no more burdensome than it would be for a traditional hard copy consent process.

Although it is not a legal requirement to provide study information in writing (whether this refers to a hard copy or digital PIS), potential participants (and/or their legal representative where appropriate) should be provided with access to written information about the study for the purpose of seeking informed consent, either as a physical hard copy or digital download. Participants can then use this in conjunction with the interview to help them reach an informed decision.

Participants (and legal guardians where appropriate) should also be provided with a copy of (or have access to) their signed and dated consent form (either electronically or on paper).

Where a hardcopy of the information is provided via an e-consent system, this must contain sufficient information regarding the nature, significance, implications and risks of the trial and explain the participant's right to withdraw at any time. However the hardcopy PIS does not need to reproduce multimedia content contained in the e-consent information.

6.2.2 Recording consent in CTIMPs

For CTIMPs, the participant's (or legal representative where applicable) consent must be recorded in writing, dated and signed, or otherwise marked by the participant. 'Writing' is defined in UK law as 'typing, printing, lithography, photography and other modes of representing or reproducing words in a visible form'. It does not necessarily have to be on paper.

Where the participant has capacity but is unable to indicate their consent by signing (either by wet ink or electronic signature) then their consent may be given orally in the presence of at least one witness and recorded in writing. This method must be approved by a REC.

6.2.3 Electronic signatures in CTIMPs

The type of electronic signature that should be used will depend upon the specific context and risk of the trial.

For most CTIMPs (and other research involving more than minimal risk/burden/intrusion), simple e-signatures that involve the participant tracing their handwritten signature using a finger or a stylus or biometric e-signatures should normally be used as they allow for direct comparison with e-signatures and/or wet ink signatures previously used by the participant for the purpose of audit or where the consent is contested.

For type 'A' CTIMPs (where the risk is no higher than that of standard medical care) any simple e-signature may be used. This may involve the participant tracing their handwritten signature using a finger or stylus or biometric e-signatures. Typewritten or scanned signatures may also be used with sponsor and HRA/REC approval. Regardless of the use of a simple e-signature, verification of the participant's identity must be confirmed.

For type B (where the risk is somewhat higher than that of standard medical care) and type C (where the risk is markedly higher than that of standard medical care) trials, simple e-signatures (e.g. finger drawn stylus or biometric e-signature) may be

used however typewritten or scanned images must not be used. Verification of the participant's identity must be confirmed. Where the participant is not known to the research team, there should be an auditable trail to demonstrate trust of the identity of the signatory.

A specific situation or type of trial may require the use of 'advanced' or 'qualified' electronic signatures in order to provide greater assurance that the documentary evidence does indeed represent the consent of the specific participant it purports to (e.g. where the trial is to be conducted entirely remotely and face to face verification is not possible).

Where consent is given remotely the investigator should ensure the e-consent process allows for discussion and ample opportunity to ask questions. This may utilise phone calls or secure video consultations (e.g. via 'Attend Anywhere'). If the participant is required at some point to visit the site for study purposes, then verification can be done in person provided this is done prior to receiving any intervention (this should be documented in the patient records). If clinical trial activities are solely conducted remotely, it may not be possible to verify who the participant is in person, therefore an advanced or qualified e-signature should be used.

The HRA/MHRA joint statement provides examples of e-consent scenarios for: 1) a Type B or C CTIMP where the consent process takes place in person at site and 2) CTIMP where the patient is remote at the time of consent.

6.2.4 Some additional conditions for using electronic methods to seek and document informed consent in CTIMPs (please note some points below apply to all research – this has been clearly indicated)

- The signature must be dated either manually by the participant or automatically by the e-consent system (applies to all research)
- Non-editable copies of the PIS/ICF should always be provided to participants. It must be possible to verify which version of the PIS and ICF the electronic signature applies to (applies to all research)
- Methods must be in place to ensure that the person signing the electronic consent form is the person who will be participating in the research study (applies to all research)
- The source consent documentation (including audit trails and metadata) must be stored in the ISF and must be available for inspection during and after the end of the trial according to the legally required retention period
- Access to the e-consent system must be readily available to auditors, inspectors and monitors both during and after the end of the trial (applies to all research)

- The site team must be able to retain control of the informed consent process and documentation so that personal identifiable data are not inappropriately disclosed beyond the site to sponsors or third parties (applies to all research)
- Where a sponsor has commissioned a third party to provide an e-consent system, the necessary information governance arrangements must be in place to ensure participant confidentiality is protected with appropriate access and retention controls to the system. Where the sponsor is responsible for auditing, ensuring compliance, and maintaining access controls to the e-consent system they may provide the appropriate certifications to the site as needed (applies to all research)
- Personal identifiable data should not be disclosed beyond the site unless explicit agreement has been sought from the sponsor, local site and the patient has consented to this. GDPR and local policies must be followed (applies to all research)
- A copy of the informed consent documentation (PIS & ICF) must be provided to the participant and retained in the ISF (applies to all research)
- MHRA inspectors must be able to access the e-consent system in a readily available way during triggered, short notice or unannounced inspections.
- Where advanced or qualified electronic signatures have been used, an inextricable link must be maintained between the metadata and the document, thus demonstrating the electronic signatures authenticity for as long as applicable legislation requires, dependent on the type of trial.

6.3. Seeking e-consent/remote consent in other research

For non-CTIMPs, although it is not a legal requirement to provide written information or document consent in writing, it is considered best practice and so investigators must document consent unless not doing so can be justified (and approved by the sponsor, NJRO and a REC).

Participants with capacity who are unable to physically sign a paper or electronic document may provide consent orally or by any other means of communication. Again this must be approved by the sponsor and a REC.

6.3.1 Electronic signatures in non-CTIMPs

For the majority of non-CTIMP research involving only negligible or minimal risk (e.g. face to face surveys / non-sensitive qualitative research), any simple electronic signature is normally adequate where it is approved to seek consent (including typewritten or scanned e-signatures).

Where the research involves more than minimal risk/burden/intrusion simple e-signatures that involve the participant tracing their handwritten signature using a finger or stylus or biometric eSignature should be considered as they allow for direct comparison with e-signatures and/or wet ink signatures previously used by the participant.

For postal/online surveys or self-administered questionnaires where identifiable personal data are collected, and consent used as the legal basis for the purposes of GDPR compliance, then the participant must be able to actively signify their consent. This can be achieved by providing an explicit consent statement and a tick box within the survey/questionnaire that the participant can complete if they are in agreement. A handwritten/biometric eSignature is not necessarily required.

6.4 Use of e-consent/remote consent in NuTH sponsored studies

If a CI wishes to incorporate e-consent/remote consent in to their study design, this must be highlighted to the NJRO sponsor team before any funding application is submitted. It should be made clear when completing the Project Initiation Form (PIF) which is then reviewed by the NJRO sponsor team. The sponsor team can then assess the feasibility of using e-consent/remote consent within the proposed study which will also feed in to whether provisional sponsorship can be confirmed. Some aspects to consider when reviewing an e-consent method from a sponsor perspective are included within Appendix 1, although please note this is not an exhaustive list.

The time needed to develop and set up e-consent/remote consent processes should be factored in to the study setup timeline. For instance, the CI should consider additional time for any necessary vendor assessments, contracting, e-consent system development, validation and user acceptance testing, appropriate site feasibility assessments, e-consent training etc. The sponsor team can advise on this during application meetings or via email as appropriate.

Electronic methods for seeking informed consent must be documented in the study protocol and appraised at the study risk assessment. Appropriate risk mitigations will be implemented by the sponsor team, which may include the development of a QA strategy (e.g. application of a computer system validation review for an e-signature / audit of the e-consent process) and/or monitoring strategy (e.g. targeted monitoring of the e-consent/remote consent process).

If CI's wish to utilise any third party vendors as part of e-consent provision, approval must be sought from the sponsor team. The sponsor team will conduct a vendor assessment where appropriate. Some aspects that will be considered within the sponsor vendor assessment include:

- Vendor policies and procedures for storing and archiving approved documents
- Data security, access & storage (only the site should have access to signed consent forms)
- Ability to access paper based versions of e-consents
- Audit trail – capture revisions, person making changes, reason for changes and date the changes were made.

It is also important that any e-consent/remote consent methods contain appropriate version control so it is clear what version of the consent form has been signed and when, and also what PIS version the patient has received.

All versions of the e-consent form should be available throughout the study and following archiving for monitoring, audit and inspection purposes. Similarly, if patients are required to re-consent throughout the trial, all versions of e-consent forms signed should be available and accessible.

It is also vital to incorporate contingency planning within the study risk assessment / monitoring plan (as appropriate) to ensure that if technical disruptions or failures arise in relation to the e-consent system, there is a contingency plan for the consent process.

Appropriate e-consent/remote consent training for sites is also vital during the site set up process and should be incorporated in to Site Initiation Visit (SIV) information. All relevant staff must be trained on the e-consent/remote consent process before sponsor green light can be given.

The acceptability of e-consent/remote consent methods at site level must be explored within the site feasibility assessments. The use of e-consent/remote consent is still quite novel throughout the NHS therefore different sites may have different requirements and capabilities.

It may be useful to develop an e-consent/remote consent manual for sites to use, which may detail the process for user training/certification; process for consent printing; process for archival; contact information for assistance; and back up process in case of system failure.

7. References

EU regulation No 910/2014 is supplemented by the Electronic Identification and Trust Services for Electronic Transactions Regulations 2016 (SI 2016/696) (the UK eIDAS Regulations) http://www.legislation.gov.uk/uksi/2016/696/pdfs/uksi_20160696_en.pdf

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MHRA GXP Data Integrity Guidance and Definitions. Revision 1, March 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

TransCelerate Biopharma eConsent Implementation Guidance. V1.0 (2017) http://www.transceleratebiopharmainc.com/initiatives/econsent/

U.S. Food and Drug Administration. Use of Electronic Informed Consent in Clinical Investigations, Questions and Answers. Guidance for Institutional Review Boards, Investigators, and Sponsors (December 2016) https://www.fda.gov/downloads/drugs/guidances/ucm436811.pdf

8. Appendices

Appendix 1 - Some sponsor considerations when reviewing an e-consent/remote consent system (please note this is not an exhaustive list):

Operational Considerations Both electronic and paper based process available to use? Ability to document process used in EDC system? Can the EDC system highlight any non-compliances with the e-consent process? Access to ICF browser independent if patients are expected to use their own devices? Provision of devices clear and appropriate (if appropriate)? Access to ICF browser if activity is taking place in patient homes or on site? Is there a contingency plan in case the e-consent system experiences technical failures? Does the e-consent process involve an interview with participants where required and does this align with local e-consultation methods at sites? Does e-consent/remote consent align with the visit schedule? (e.g. consider if the participant needs to attend hospital for baseline visits and thus whether remote consent is an appropriate option, or whether this can be done on site)
Roles and Responsibilities How is version control managed with regards to the e-consent documentation? How are different languages managed (where appropriate)? Who is hosting the eICF software application and is a vendor assessment required? Are appropriate information governance arrangements in place to protect participant confidentiality? How is website access controlled? How are questions created and answered? What happens if the website is down temporarily? Who is managing the user accounts and are these issued only after e-consent training?
Subject Authentication

Can the signature be attributed to the person participating in the trial and can this be demonstrated via audit trail for inspection purposes? Is there a verification step to ensure this? Subject cannot repudiate/delete the signature once invoked? Any person cannot alter the consent form once fully signed? Signatures time/date stamped, either manually by the participant or automatically by the e-consent system? Can the electronic signature only be applied by the owner of that signature? Is it possible to verify which version of the PIS and ICF the electronic signature applies to? Is there ongoing opportunity to document continued consent?
Accessibility Appropriate access and retention controls in the e-consent system? Is the eICF printable as a non-editable PDF? Can the patient access a non-editable copy of the PIS (containing information on the nature, significance, implications and risks of the trial, and right to withdraw from the trial at any time) and ICF? Do patients have a contact for further information about the trial? Can you ensure the patients had enough time to consider the trial? Can this be accessed for monitoring, audit and inspection purposes at short notice? Can source consent documentation (including audit trails and metadata) be stored in the ISF and be available for audit/inspection purposes? Is access to the e-consent system readily available to auditors, monitors and inspectors both during and after the trial? Can the site team maintain control of the informed consent process/documentation so that personal identifiable data are not inappropriately disclosed beyond the site to sponsors and third parties?
Other Is it feasible/appropriate to use e-consent/remote consent in the study population? (i.e. e-consent methods should not discriminate against those who are not comfortable or who cannot use such technology) Consider whether sufficient time has been factored in to the setup of the study to develop the e-consent system and conduct all necessary sponsor assessments? Has the feasibility of e-consent been assessed with sites? Is contracting/vendor assessments required with third party e-consent providers? Is an assessment needed from information governance? Validation and user acceptance testing considered? Has a sufficient e-consent/remote consent training package been developed? Is the e-consent/remote consent process appropriately documented throughout the study documentation (e.g. protocol, application, PIS, risk assessment, monitoring plan etc.)? Is an e-consent study manual required? Does the e-consent/remote consent process comply with the principles of GCP? Has the e-consent system been appropriately costed (where appropriate)? (consider any financial impact on the funding application/grant)

Appendix 4: NJRO REDCap Remote Electronic Consent

Newcastle Joint Research Office

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

NJRO REDCap Remote Electronic Consent

NJRO-INF-SOP-003

Newcastle Joint Research Office

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

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Newcastle Joint Research Office

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

1. Background/Introduction

Electronic Consent (eConsent) is the process of seeking, confirming and documenting informed consent in research studies using electronic means. Remote Electronic Consent is an extension of this, using electronic systems to consent without the patient being required to physically attend a research appointment.

The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) offers the facility to electronically and remotely consent via NJRO REDCap for research projects in accordance with HRA and MHRA guidance **(7.1)**.

This SOP should be used in conjunction with NJRO REDCap Data Security SOP **(8.1)**.

2. Purpose

To describe the responsibilities of NuTH and NJRO REDCap Project Administrators when using NJRO REDCap to conduct electronic consent.

3. Scope of Document

Applicable to all staff using NJRO REDCap to electronically consent.

4. Definitions

CTIMP - Clinical Trial of an Investigational Medicinal Product
HRA – Health Research Authority
MHRA – Medical and Healthcare products Regulatory Agency
NJRO – Newcastle Joint Research Office
Project Administrator – Point of contact provided to the NJRO for a specific NJRO REDCap project/study

5. Roles & Responsibilities

It is the responsibility of all Project Administrators to ensure their eConsent process meets the guidance set out by relevant health and research organisations.

6. Procedures

6.1. System

- Remote eConsent can only be performed via Internet REDCap

6.2. Local approvals

- The intended type of eConsent must meet requirements dependant on the nature of the project/study, as set out by the HRA and MHRA **(7.1)**
- The intended eConsent process must receive all usual approvals (e.g. ethical approval, Caldicott) before consent can take place via REDCap.

6.3. Authentication

- All eConsent forms must utilise the 'Survey Login' feature on REDCap, which requires participants to input one or more identifiable fields (e.g. date of birth) to authenticate their identity

6.4. Form design

- eConsent forms will be created with support from the NJRO Informatics Team
- eConsent forms must utilise the REDCap eConsent Framework
- There is no prescriptive eConsent form design, however they must include at a minimum:
  - Project title (descriptive field)
  - Consent form version number (drop-down field)
  - Patient information sheet version number (drop-down field) (where applicable)
  - Consent questions (checkbox fields)
  - Patient's full name (text field)
  - Patient's signature (e-signature field)
  - Date of consent (date field)

6.5. Staff signatures

- When necessary, signatures from staff taking consent will be captured in an accompanying attestation form(s)
- Accompanying attestation form(s) will be automatically combined with the signed patient consent form via the 'Multi Signature Consent' external module **(7.2)** to form a fully consented PDF document, stored in a file upload field in the REDCap project

6.6. Patient copies

- The REDCap alert system must send out an automatic e-mail copy of the fully consented PDF document to the patient upon creation

6.7. Additional PDF copies

- It is the responsibility of Project Administrators to ensure additional copies of the consent form are downloaded and utilised when necessary (e.g. to update a patient record)
- Additional PDF copies can be downloaded via the file upload field by nominated individuals. It is the responsibility of these individuals to ensure PDF copies are downloaded only to devices in accordance with local data protection and data security compliance

6.8. Version control

- New versions of the eConsent form will be created as a new eConsent instrument within REDCap
- Expired versions of the eConsent form will be deactivated upon activation of a new eConsent form

7. References

7.1 MHRA and HRA Joint statement on seeking consent by electronic methods https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf

7.2 Multi-Signature Consent REDCap External Module https://github.com/susom/multi-signature-consent/

8. Appendices

8.1 NJRO REDCap Data Security SOP https://g14784.gael-config.net/QPulseDocumentService/Documents.svc/documents/active/attachment?number=NJRO-INF-SOP-002