Study Title: The creation of a UK myasthenia database

Ethics Ref: 22/SS/0093
IRAS Project ID: 312598

Date and Version No: 15/12/25, version 1.8

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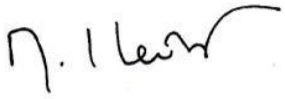

Statistician Signature: Not applicable: Not an interventional study

Declaration of conflict of interests:

I can declare that there are no conflicts of interest for any involved parties.

Confidentiality Statement
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. KEY CONTACTS

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2. LAY SUMMARY

Myasthenic syndromes are a group of diseases affecting the communication between the nerve and muscle. They result in weakness of a variety of muscles including those that move the eyes, those that control swallowing and breathing and those that move arms and legs. The three main categories are myasthenia gravis, Lambert-Eaton myasthenic syndrome and the congenital myasthenic syndromes. The former two are caused by antibodies targeting the neuromuscular junction while the latter is due to a variety of genetic mutations. They affect all ages, from infants to the elderly, and can have a huge impact on the lives of patients.

These conditions are all rare, making research challenging. Furthermore, there is no accurate estimation of the epidemiology of these conditions in the UK. To address this shortcoming, we are proposing to create a UK database containing information on the demographics and clinical aspects of all patients with these conditions in the UK who agree to be included. This data will then be made available to researchers around the UK in an anonymised form. Analysis of this data will then allow for improved, up to date epidemiological data and a better understanding of the disease burden in the UK. Furthermore, this data will aid the identification of trends in the disease that may change diagnosis and treatment and inform further research in the future. The result of this will be better treatment for patients and more targeted research in the future.

The database is intended to be maintained indefinitely allowing ongoing collection of data for up-to-date epidemiological data as well as identification of emerging trends in the diseases over many years.

3. SYNOPSIS

Study Title	The creation of a UK myasthenia database.
Internal ref. no. / short title	UK Myasthenia Database
Study registration	N/A Non-interventional study
Sponsor	University of Oxford Research Governance, Ethics and Assurance Address: Joint Research Office Boundary Brook House Churchill Drive Headington Oxford OX3 7GB

Funder	Myaware		
Study Design	Observational study		
Study Participants	All patients treated under NHS hospital care for a diagnosis of myasthenia gravis, Lambert-Eaton myasthenic syndrome or congenital myasthenia.		
Sample Size	Estimated 20,000		
Planned Study Period	Project is initially planned to start September 2022 and run until at least September 2024, however the intention is for the database to be maintained indefinitely with regular updates of patients going forward.		
Planned Recruitment period	Start date: 1st September 2022 End date: 30th September 2028		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Create and populate a research database containing data on patients with a diagnosis of MG, LEMS or CMS under NHS hospital care in the UK.	Successful creation and population of database.	Start data collection: September 2022 Data from all UK by July 2023 (earliest) Regular updating of data: August 2023 onwards
Secondary	Data to be made available to UK research teams for clinical/social research or audit.	Release of data and outcomes will depend on the requests from research teams and will be decided on a case-by-case basis.	September 2022 onwards
Intervention(s)	No intervention		
Comparator	N/A		

4. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
RGEA	Research Governance, Ethics and Assurance
GCP	Good Clinical Practice
GP	General Practitioner

HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
MG	Myasthenia Gravis
LEMS	Lambert-Eaton myasthenic syndrome
CMS	Congenital Myasthenic Syndrome
REDCap	Research Electronic Data Capture

5. BACKGROUND AND RATIONALE

Myasthenic disorders are rare chronic conditions of the neuromuscular junction that include myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS) (Gilhus and Verschuuren, 2015) and the congenital myasthenic syndromes (CMS) (Newsom-Davis, 2007).

MG is caused by different types of autoantibodies targeting the postsynaptic muscle membrane, more frequently against the acetylcholine receptor (AChR), followed by those against the muscle specific kinase (MuSK) (Leite *et al.*, 2010), whereas a smaller proportion of patients have antibodies to clustered AChR (Leite, 2008); there are recent reports of patients with MG associated with antibodies against LRP4 (Pevzner *et al.*, 2012). Around 15% of adult patients with MG with AChR antibodies have thymoma. MG affects patients of any gender and at any age, although adult population are more frequently affected. Patients with autoimmune myasthenia rely on chronic, and sometimes also acute, immune treatment (Sussman *et al.*, 2015). Thymectomy is indicated in MG patients with AChR antibodies and disease onset before the age of 50 or 55 years and in those with thymoma regardless their age (Wolfe *et al*, 2016).
LEMS is caused by autoantibodies to the presynaptic voltage-gated calcium channel (VGCa). It affects mainly adults, around half of them having a form of lung malignancy (Eaton and Lambert, 1957; Schoser *et al*, 2017). Treatments are similar to those in MG, in addition to 3,4-DAP (Maddison *et al*, 2017).

CMS are a heterogenous group of very rare genetic conditions caused by mutations in genes that are essential for neuromuscular conditions (Rodríguez Cruz *et al.*, 2018); to date, more than 30 different subtypes of CMS have been identified. CMS is more likely to present at early ages though it can present in adults. These conditions are usually challenging to treat, although new therapies have been developed recently (Rodriguez Cruz *et al*, 2015).

Demographic characteristics of the patients with myasthenic disorders, in particular those with AChR antibodies, have been changing over the last three decades, with a steady increment in the number of patients with the disease onset over the age of 50 years (Carr *et al,* 2010). Studies from countries where national registries are well established suggest that improvement in the diagnosis and general medical care of myasthenic disorder patients has resulted in a marked reduction in mortality and a subsequent epidemiological change driven by a marked increment in disease prevalence, particularly in adults, who also survive to other morbidities (Casetta *et al*, 2010 and Breiner *et al.*, 2016). However, the overall epidemiology data of myasthenic disorders is highly variable with studies showing marked variation with respect to the incidence, prevalence and mortality figures of myasthenic disorders. In the UK, 7 studies have been performed between1950 and 2007, which may not reflect current epidemiology (Carr *et al*, 2010). Among them, a population-based study showed a prevalence of 15 per 100,000 population and incidence of 1.1/100,000 population/year (Robertson *et al*, 1998). There are no epidemiological studies on MG with MuSK antibodies in the UK. Little is available on the epidemiology of LEMS in the UK. The prevalence of genetically confirmed congenital myasthenic syndromes in the UK has been estimated to be 9.2 per million children under 18 years of age (Parr *et al*, 2014), while there is no current data on the adult population with CMS.

In the last 20 years, there have been important therapeutic advances in autoimmune as well as in rare genetic conditions which include myasthenic disorders. However, their implementation in our regular clinical practice is still suboptimal and vary from region to region in the UK. Moreover, there are still questions on whether new treatments (e.g. monoclonal antibodies) are effective in all patients or only in some subgroups, and when they should be started and stopped (Evoli A, 2017). In addition, there is not enough data to understand the long-term outcome and safety profile of the new therapies, particularly in the autoimmune myasthenic disorders.

UK specialised myasthenia centres have been collecting relevant clinical information, which they store in appropriate databases managed locally, and they may share their anonymised data with other centres, according to their ethical approval, for collaborative studies. However, there are no well-stablished national registries or national databases of myasthenic disorder patients in the UK. As a consequence, (1) there is only a very limited number of publications on demographic and epidemiological figures for myasthenic disorders across UK; (2) there is incomplete knowledge on the spectrum of clinical presentations, course of the disease, severity of clinical symptoms, impact of co-morbidities (e.g. malignancies, other autoimmune conditions), treatments used, as well as their effectiveness and complications (e.g. diabetes and other diseases as vascular risk factors), and overall disease outcome, including complications, morbidity and mortality of these conditions in the UK; (3) there are no accurate UK records on pregnancies in patients with myasthenic syndromes, including pregnancy outcomes and disease activity during pregnancy; (4) there is no reliable information to identify the overall medical needs of patients with myasthenic disorders, including their requirements and suitability for new treatments or even recruitment for national or international clinical trials; (5) there is insufficient information to study the significance and burden of the myasthenic disorders at the individual level or general healthcare provision associated with both direct costs (e.g. long-term treatment, acute treatment, primary care reviews, hospitalizations) and indirect costs (e.g. income loss and reduced caregiver productivity) in the UK.

OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective Create and populate a research database containing data on patients with a diagnosis of MG, LEMS or CMS under NHS hospital care in the UK.	1) Recruit all hospitals in the UK and populate database with data for patients under hospital care for myasthenic syndromes in the UK. A more comprehensive summary of the data to be collected is listed in appendix A.	Completed by September 2024
Secondary Objectives Data to be made available to UK research teams for clinical/social research or audit.	Release of anonymised data and outcomes will depend on the requests from research teams and will be decided on a case-by-case basis.	April 2023 onwards
Additional Objectives Generate research publications and audit using data in database.	Outcome measures will depend on the individual research/audit projects.	April 2023-onwards

6. RESEARCH DATABASE DESIGN

1) Using Research Data Capture (REDCap) software, hosted by the University of Oxford Medical Science Division, the database manager will create a database to collect information on demographics, clinical syndromes, investigations, treatments and related comorbidities of patients with myasthenia gravis (MG), Lambert-Eaton myasthenic

syndrome (LEMS) and congenital myasthenic syndromes (CMS). The data to be collected is outlined in the data dictionary (appendix A).

2) The database manager's role will also include:
    a. Communicating with individual hospitals to coordinate data entry from additional sites.
    b. Maintenance and monitoring of the database.
    c. Data entry.
    d. Managing data access of other users.
3) There will be multiple meetings of a steering committee that includes the team at Oxford, several neurologists across the UK at collaborating centres (Belfast, Glasgow, Birmingham, London, and Southampton), two patients and a representative of the trustees of Myaware. Here, the data to be collected will be discussed and potential challenges to data collection addressed. Any concerns will be noted and addressed.
    .
4) Establish who will collect data at collaborating data collection centres. This will be arranged via collaborating consultants and their local clinical teams.
    a. Those selected for data entry will apply to Oxford medical science division (MSD) for REDCap access and will be given a unique username and password.
    b. Access will be controlled by the database manager. This is detailed further in section 11.2.
5) Awareness will be raised about the creation of the database. This will be done via by letters, leaflets, social media and Myaware website. Database manager will also attend Myaware member Zoom calls to speak directly to patients and address questions.
6) Patient consent will be sought and patient data entry into REDCap database will begin.
    a. Approval will be sought from the Research and Development department and, where required, Caldicott guardian of individual trusts who will be entering patients into the database where necessary.
    b. An initial trial run of patient data entry will first take place at Oxford University Hospitals and two collaborating sites selected at the time, with real patient data being entered by the database manager and other members of the Oxford clinical teams. This will be used to ensure that the database is working as planned.
        i. Patients consent will be obtained before data is entered.
        ii. Data for 30 eligible patients treated at each of Oxford University Hospitals and the two other collaborating sites will be used for the trial period.
        iii. If the trial run is successful, data entry will be expanded to include other sites and the data for the remaining Oxford University Hospital patients will also be entered.
        iv. If the trial run identifies any issues, these will be addressed, any relevant updates to documentation made, and the trial run repeated until results are satisfactory.
    c. Expanded data collection will then take place, including remaining main collaborating sites (see listed investigators above), before expanding to include others NHS trusts over time.
    d. Data will be stored on University of Oxford MSD IT REDCap servers.
    e. Prior to any data entry, written informed consent will be obtained by the clinicians responsible for patient care.
        i. Patients will be provided with written information.
        ii. Original signed consent forms will be stored at the patient's local hospital in their medical notes.

iii. The consent form will include entry into the database and desire to be contacted about future research as separate consents.
iv. A copy of the consent form will be securely emailed to the database manager or coordinator for central storage in the master file for the database on a secure MSD IT server.
v. A copy of the consent form will be given to the patient either in person or securely via email or post.
vi. A remote consent form is also acceptable as an alternative.
vii. For those aged 11-15 years who are able to understand, an assent form is required in addition to a consent from signed by their parent or guardian.
viii. When the patient turns 16, they will be asked if they wish to continue having their clinical data held by the research database. At this point, they will be given the adult PIS and asked to consent for themselves.
ix. The person entering patient data will be required to confirm consent has been obtained on REDCap.

f. Data will be collected from hospital patient records (electronic or paper) and entered by members of the clinical team caring for the patient.
g. Data to be collected will be selected so that it is present in the majority of patient records and is unlikely to require additional patient contact. However, should key information be absent, it will be at the discretion of the clinical team responsible for the patients care to obtain this information when they next speak with the patient.

7) In parallel to 5, other NHS hospitals will be liaised with to identify additional collaborators and to prepare for data entry at other hospitals.
   a. Those who will be contacted to identify patients and enter data will include:
      i. Neurologists responsible for patients with myasthenia.
      ii. Paediatricians responsible for patients with myasthenia (likely to be paediatric neurologists in most cases).
      iii. Ophthalmologists/Neuro-ophthalmologists responsible for patients with ocular myasthenia.
8) Data will gradually be entered from other NHS hospitals/trusts around the UK until as close to all eligible patients as possible are entered.
9) Once a patient's initial data entry is completed, an additional form on the REDCap database will be used at subsequent follow up appointments to update their information.
10) In order to estimate the coverage of the database, the clinical practice research datalink (CPRD) will be used to estimate the percentage of patients with MG, LEMS and CMS under primary care but not hospital care. This will be accessed via the Nuffield Department of Public Health.
11) Once the database is populated, it will be possible for research teams across the UK to apply for access to anonymised data:
   a. This will be done via an application form (see separate document).
      i. In addition, the requesting researcher will be required to select the exact data they require from an attached list.
   b. The request will be discussed by a data access committee, chaired by the CI, who will review the intended use of the data.
   c. Data will not be made available for commercial use.
   d. For practical purposes, the entire committee need not be present for a decision to be reached. A minimum of three doctors and one patient representative must be included.

e. If the committee agrees, the data will be anonymised and downloaded by the database manager as a spreadsheet. All data will be anonymised as far as is possible, with hard identifiers removed as a minimum.
f. A risk analysis of the anonymisation will be undertaken either using the UKAnon Framework, or the ICO's guidance. If required, appropriate safeguards will be written into a sharing agreement with the third party.
g. Only the minimum data required for the intended research will be made available.
h. Before any data is shared, a data sharing agreement (see separate document) will be signed.
i. The data will then be transferred to the applicant using the secure University of Oxford Nexus 365 OneDrive software. This document will be password protected. The password will be provided via SMS text message.
j. If a member of the committee is requesting access to the data, they will be excluded from the decision-making process to avoid conflict of interest.
k. Any data provided for research will need to be destroyed after 5 years, or an extension applied for.

12) Once the database is populated, researchers looking for patients to be included in the database can apply using a study participant identification request form. Any research must have all necessary regulatory approval in place.
    a. The application will be discussed by the data access committee.
    b. If the data access committee agree, then patients who have given consent to be contacted about future research and who meet the desired inclusion criteria of the study will be identified.
    c. The clinical team of these patients will then be contacted to inform them that they may be eligible for a study, and they will be given the necessary information to pass on to the patients. If the patients are interested in the study, they will then go through the approved recruitment process of that study.
    d. At no point during this invitation to participate will the patient be contacted by the applying research team or the central database team.
    e. No information regarding eligible patients will be provided to an applying research team.

7. PARTICIPANT IDENTIFICATION

7.1. Study Participants

All living patients with a diagnosis of myasthenia gravis, Lambert-Eaton myasthenic syndrome or congenital myasthenia that live in the UK and are under the care of the NHS hospitals for their myasthenia will be eligible for the database. These patients are expected to be under the care of neurology, paediatrics, neuro-ophthalmology or ophthalmology.

If living patients already in the database become deceased, the database will be updated to record this and if possible, their cause of death.

Inclusion Criteria

Patients of all ages (ranging from infants to the elderly), gender and disease severity will be entered as long as they have a diagnosis of myasthenia gravis, Lambert-Eaton myasthenic syndrome or congenital myasthenia and are under hospital care.

Patients must be willing and able to give consent or have a parent or guardian to consent on their behalf.

7.2. Exclusion Criteria

- Already deceased.
- Patients under primary care only.
- Adults unable to consent for themselves.

8. PROTOCOL PROCEDURES

8.1. Recruitment

Identifying recruitment/data collection centres:

- To begin with, UK myasthenia centres only will help identify patients who meet the eligibility criteria.
    - These will be selected from recognised myasthenia centres from around the UK to provide broad coverage of the UK for initial data entry.
    - The initial participating centres have already been identified as collaborators (identified under the heading Investigators above).
- Later, this will be expanded to include other myasthenia centres across the UK. Consultants from these hospitals will be contacted throughout the project.
- Other hospitals where patients with myasthenia are treated, but who are not recognised myasthenia centres will then be contacted so that they can begin data entry.

Identifying patients:

- Most centres have their own database/spreadsheet recording their patients with myasthenia or will have other methods of identifying suitable patients depending on their local system. (e.g. searching their electronic patient records for patients with a diagnosis of myasthenia gravis, Lambert-Eaton myasthenic syndrome or congenital myasthenic syndrome).
- In addition to the above, data can be entered as patients return for follow up. As we expect all patients under hospital care to be having some form of follow up, this should lead to all patients ultimately being identified.

Approaching patients:

- Patients will be approached by their local clinical team.
    - This will either be done during routine clinic appointments, while they are an inpatient, or by telephone call. The exact method of approaching patients will be done at the discretion of the local team depending on the circumstances.
- They will be provided with written information and written consent will be obtained by a member of the clinical team for their data to be entered into the database. This consent may be signed in person or completed remotely.
- For those under the age 16, a parent or guardian must consent on their behalf. For those able to understand, an assent form should also be signed.

Screening and Eligibility Assessment

- Screening will be performed by the clinical team responsible for the patient's normal care.
- There is no maximum duration between screening and registration.
- Participants must satisfy all inclusion and exclusion criteria of the protocol to be included.
- Changes to the approved inclusion & exclusion criteria may be made by substantial amendment only.
- The screening procedure will include:
    - Reviewing medical history to confirm a diagnosis of MG, LEMS or CMS.
    - Reviewing records to ensure patient is alive.
    - Ensuring patient is able to consent if they are an adult or, if a child, that they have a parent/guardian to consent for them.

8.2. Informed Consent

- Patients will be provided with written and verbal information by their local clinical team detailing the exact nature of the study, what it will involve, the reasoning for it and any risks involved. It will be made clear that they have the right to withdraw at any time without question and without being required to give a reason. They will be given opportunities to ask questions and have as much time as they wish to consider their decision.
- A simplified version of the participant information sheet and assent form will be available for young patients aged 11-15 or others who may want it, and a participant information sheet for those under 11 years of age.
- The patient/parent/guardian must then sign and date the latest version of the consent form. This will be obtained by the clinical teams caring for the patient either during routine clinical appointments or remotely depending on what is most feasible. The person obtaining the consent will be a suitably qualified and experienced person who is authorised by the CI/Database manager to do so.
- For the process of remote consent, patients/parents/guardians will be provided with the relevant participant information sheets and a remote consent form either by email or post and given time to read through this. Consent will then be taken either via telephone or video and the person taking consent will complete the consent form with the participant/their parent or guardian's responses.
- The consent form will include separate consent for entry into the database and whether they agree to be contacted regarding future research.
- In all cases, a copy of the consent form will be given to the participant at the first opportunity. For those providing consent remotely, this will be by secure post or email.
- All signed consent forms will be stored at the patient's local hospital in their medical file. and a copy will be added to the patient's clinical notes (either physically or scanned and stored electronically).
- A copy of the consent form will also be emailed securely to the database manager or coordinator for storage in the master file for the database.
- The person entering the patient data into the database will be required to confirm that the patient has been consented before any data is entered.

- For patients or their guardians who cannot understand the English information sheets or consent forms, or who have other barriers to communication, an appropriate interpreter will be used if possible. This will be provided by the trust.

8.3. Enrolment

Patients will be enrolled by their local clinical team. Registration is automatic once they have consented and their data is entered into the database.

8.3.1. Description of study procedure(s)

Data will be entered onto a REDCap database by clinical staff or appropriately trained administrative staff. This database is accessed via a secure website (**https://redcap.medsci.ox.ac.uk/**) They will then be required to enter their unique username and password to log in. When opened, the database will contain a list of instruments each containing a selection of data fields that need completing (see appendix A). The instruments that need completing will vary depending on the patient's diagnosis. The data should be available in the patient's records in the vast majority of cases. There are no clinical procedures outside of those a patient would have as part of their standard clinical care will be required.

A data flow diagram is available in appendix B.

8.3.2. Study Visit

There will be no study visits. Data will have already been collected in routine clinic appointments and no additional visits should be required. Should additional information be required, these can be obtained from clinic appointments arranged as part of standard clinical care.

8.4. Subsequent Visits

Data will be updated following standard clinical reviews as the patient requires. No additional visits will be planned.

8.5. Early Discontinuation/Withdrawal of Participants

- Early withdrawal of a patient by the research team may occur due to ineligibility (either arising during the study or retrospectively having been overlooked at screening), or due to a patient withdrawing consent. In this case, all patient data will be erased from the REDCap database. It will not be feasible to remove previously extracted anonymised data from these patients that has already been provided to researchers. However, as the number of withdrawals for any reason are expected to be small relative to the number of patients in the database, this is not expected to be an issue when data is analysed and statistical analysis will be used to account for this.

- Due to the nature of a research database, if participants choose to withdraw, any previously extracted anonymised data that has been shared with researchers will be retained. It is necessary to retain a copy of the data shared for purposes of research integrity. However, all other patient data will be permanently erased from the REDCap database.

- A record of the number of patients who withdraw and what their diagnosis was will, however, be kept as this information may be required for future statistical analysis.

8.6. Definition of End of Study

The research database has no definite endpoint; the intention is for the database to remain live and be updated indefinitely, subject to 5 yearly REC renewals and adequate funding.

9. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate data management document in use for the study.

9.1. Source Data

Source data will be obtained entirely from hospital records, laboratory records and radiology records. The data will be entered into the REDCap database by clinicians caring for patients. The clinicians responsible for the patient and the research team will have access to the NHS number and date of birth as identifiable information. However, once the information is extracted for statistical analysis, identifiable information will be removed and it will be anonymised as far as possible. The patients will then be referred to by a record number only.

Source data will be obtained from several source documents:

Source	Data obtained
Electronic patient records (includes correspondence).	Demographics, diagnosis, MG background (antibody status, clinical syndrome), current medication, comorbidities, recent hospital admissions, neurophysiology results.
Paper patient records	Demographics, diagnosis, MG background (antibody status, clinical syndrome), disease activity over previous 3 years, current medication, comorbidities
Consent form*	Patient's signed consent.
Laboratory result software	Antibody status, genetic test results.
Imaging software	CT/MRI/PET scan reports (no images, just reports)

Table 1: Source documents from which data collected is obtained.

Data will be collected from the aforementioned source documents. The exact software will depend on the software used at participating hospitals. This data will then be entered into a secure Research Data Capture (REDCap) database that will be hosted by the Medical Sciences Division (MSD) of the University of Oxford. Data entry will be by clinical teams caring for the patient as previously described.

9.2. Access to Data

- Complete access to the database will be available to the CI/PI and other core members of the Oxford research team (supervisors, database manager and database coordinator) as this will be required for the maintenance of the database.
- Collaborating clinicians and data enterers will be given restricted access to the database. Access privileges will be managed by the database manager and database coordinator. They will be able to access the complete data on REDCap for patients being treated at their hospital/trust only. Access to data from other hospitals will only be possible in a pseudonymised form and will be provided by the database manager once a Data Access Form (separate document provided) has been completed, reviewed and agreed to by the Data Access Panel.
- A data sharing agreement will then be signed prior to access to data being granted.
- Patients will be able to request access to their own data via a Patient Data Access Form they can request from and submit to their medical team. Their complete data can be provided as a spreadsheet for them. This will be downloaded by their medical team or, if they are unable to, the database manager/coordinator. If the database manager/coordinator download the data, they will send the data securely to the medical team via NHS mail.
- The downloaded data will be given to the patient by their medical team either in person, or securely via email or post.
- Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

9.3. Data Recording and Record Keeping

Data collection plan:

1. A data flow diagram is available in appendix B.
2. Data will be collected from collaborating hospitals across the United Kingdom. This will begin with OUH, before expanding to the main collaborating sites described above. Once this process is in place, other trusts will gradually be included until all UK hospitals are included.
3. The data will be entered by clinicians directly caring for the patients, or members of their team (e.g. junior doctors, medical students or suitably trained administrative staff).
    a. The persons entering the data will be decided by the main collaborating clinician at individual centres depending on who is available.

   b. Data enterers will be trained by the database manager in how to do this (with a written document and a pre-recorded video).
   c. Devices used to enter the data must be NHS or institutionally managed devices only.
   d. Any pseudonymised data extracted will be password protected as a minimum and transferred securely using One Drive to the intended recipient. The password will be provided via SMS message once the telephone number is validated.
4. The data will be obtained from NHS clinical records including notes, laboratory result software and imaging software (reports only) as described above.
5. Some identifiable data will be included. These are NHS number and date of birth.
   a. The DOB is required to ensure patients age remains up to date.
   b. The NHS number is required to prevent duplicate patient entries as many patients are seen at multiple hospitals or move between trusts (e.g. local district general hospital and a tertiary centre).
   c. The NHS number will also allow the local clinical teams responsible for the patients to update their information over time.
   d. NHS Number and DOB will only be visible to the clinical team looking after the patient and the team managing the database at Oxford (CI/PI, database coordinator and supervisors).
6. Other sensitive information recorded will include:
   a. Gender, ethnicity and migration status.
   b. Geographical information (the trust they are treated at).
   c. Medical information.
7. The exact data to be recorded (and therefore the exact data dictionary) may change as the database evolves and new options are created. Any new fields added to the database will be within the existing categories. Should any changes be made beyond this, then appropriate approvals will be sought from the sponsor and REC before this occurs.
8. The data will be entered directly into REDCap. This is accessed via Oxford University Medical Science Division (MSD) who will be storing the data on their secure servers.
9. All clinicians/persons who are due to enter data will be given a unique REDCap username and password.
   a. This unique account will have specific privileges that are managed by the database manager:
      i. They will be able to enter data for their patients only.
      ii. They will be able to view all data including NHS number and DOB for their patients only.
      iii. They will not be able to view wider data for the UK.
10. All patients entered will be given a unique record ID.
11. The database is currently funded until September 2024, however the intention is that this data is stored indefinitely and that the database is maintained for years to come to ensure consistent up to date information.
12. The data can be requested by researchers in the UK. If all required ethical approval is in place for their research and the data access committee agrees, they will be provided with anonymised data by the Oxford team. They will not have sufficient access to the REDCap database to re-identify database participants.
13. Due to the rare nature of the medical conditions and the detailed records being collected, it is conceivable, albeit very unlikely, that a patient could be re-identified by someone with access to hospital records. Every effort will be made to minimise this chance by providing the minimum required data, maintaining strict database access and following security protocols, as well as requiring researchers to sign a strict data sharing agreement.

14. At yearly intervals, data will be downloaded in a pseudonymised form as a spreadsheet. All strong identifiers will be removed during this process. This will be stored on the secure MSD servers of the University. Only the CI/PI, database manager, supervisor, coordinator and others directly involved with the research will have access to this. These files will be securely encrypted and password protected. .
15. All data is automatically backed up by the MSD IT servers.
16. The REDCap database data will be retained indefinitely as it is due to be updated continuously.
17. The pseudonymised data downloaded yearly will be retained for at least 10 years. Access to this data for research will be subject to the aforementioned application process and restrictions. The retention period is subject to change depending on the evolution of the database and research needs. The protocol will be updated to reflect this.

10. QUALITY ASSURANCE PROCEDURES

The database will be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

10.1. Risk assessment

A risk assessment (data protection impact assessment) has been prepared before data entry begins and will be regularly reviewed as necessary to reflect significant changes to the protocol or outcomes of monitoring activities.

10.2. Study monitoring

The environment hosting the database is subject to the University's baseline security controls which encompass monitoring and logging. The architecture, configuration and installation of the database is subject to review by the University's Information Security Team. The chosen database software - REDCap has full audit and logging facilities. The logs will be reviewed regularly to ensure that logging information is appropriate in terms of integrity, availability and detail by the database manager.

Regular monitoring will be performed by the database manager, and in future, the database coordinator, according to a study specific Monitoring Plan that is agreed in advance with the University of Oxford. Every year, a sample of five data entries from each site will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific monitoring plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

This will be done in coordination with the University of Oxford MSD IT team and Information Compliance team where appropriate.

It is University policy that appropriate information security controls are implemented to protect all IT facilities, technologies and services used to access, process and store University information. The controls required by the University are set out in the "baseline security controls". They are effectively an internal minimum standard for information security covering organisational and technical controls which are aligned industry good-practice standards such as ISO/IEC 27001:2013, PCI-DSS and Cyber Essentials.

The IT security baseline consists of approximately 80 specific requirements covering the following domains:

* Access control
* System Acquisition and Development
* Change Management
* Incident Management
* Monitoring and Logging
* Network Security
* Operational Security
* Vulnerability management

In addition to the technical controls listed, there are a series of organisational measures including security awareness training. This is mandatory for all staff and must be completed by those involved with this particular study.

The data will be processed on MSD IT servers.

10.3. Study Committees

Note: These are subject to change as people leave their roles (e.g. as Myaware trustees).

Steering Committee:

Role:

1) To agree the data that is to be collected in the database.
2) To suggest any research questions that could be answered by the database and how to do this.
3) To agree the best and most practical approach to data collection, accounting for different resources at different hospitals.
4) To ensure patient views are represented and any concerns including regarding the data to be collected, its use and storage and data protection are addressed.

Included in steering committee:

- Committee Chair and Chief Investigator - Dr Leite

- Database Manager – |Dr Mohammad Ashraghi
- 8 Myasthenia Consultants from trusts throughout the UK:
    - University College Hospital, London.
    - Imperial College Hospital NHS Trust.
    - Brighton and Sussex University Hospitals NHS Trust.
    - South Wales at Morrison Hospital.
    - University Hospital Southampton NHS Trust.
    - Belfast City and Belfast and Ulster Hospital.
    - Queen Elizabeth Hospital, Birmingham.
    - Queen Elizabeth University Hospital, Glasgow.
- 3 Patients with myasthenia gravis.
- 3 Myaware Trustees (may be same as patients).

Frequency of Meetings:

Timing of further meetings subject to progress of project. Meetings will take place via MS Teams.

Data Access Committee:

Role:

- To review requests for access to data generated by the National Myasthenia Database.
    - Review will include assessing that the criteria for data request is met.
    - To ensure that data will be used to improve the understanding or care of myasthenia.
    - To ensure that data is not being used for commercial purposes or profit.
- To agree to request so that data can be released or, if unhappy, to offer feedback to applicants.

Included in data access committee:

- Committee Chair and Chief Investigator - Dr Leite
- Database Manager – Dr Mohammad Ashraghi
- 8 Myasthenia Consultants from trusts throughout the UK:
    - University College Hospital, London.
    - Imperial College Hospital NHS Trust.
    - Brighton and Sussex University Hospitals NHS Trust.
    - South Wales at Morrison Hospital.
    - University Hospital Southampton NHS Trust.
    - Belfast City and Belfast and Ulster Hospital.
    - Queen Elizabeth Hospital, Birmingham.
    - Queen Elizabeth University Hospital, Glasgow.
- 3 Patients with myasthenia gravis.
- 3 Myaware Trustees (likely to be the same person as patients).

For a decision to be reached on data access, three consultants and one patient must review the request. These persons must not be involved in the request for data.

The persons chosen will depend on availability/conflict of interests.

11. PROTOCOL DEVIATIONS

Any study related deviation will be reported, assessed and managed in keeping with the University of Oxford standard operating procedure (SOP) number 8. All deviations from the protocol will be documented in a protocol deviation form and filed in the study master file. The study will be monitored in keeping with University of Oxford SOP number 12.

12. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor will be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving Research Ethics Committee (REC) and the relevant NHS host organisation within seven calendar days.

Suspected personal data breaches must be reported immediately to the University of Oxford's Data Breach Team: data.breach@admin.ox.ac.uk .

IT security related incidents (e.g. malware, hacks) to be reported to the University of Oxford's Information Security Team: oxcert@it.ox.ac.uk .

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The CI/PI will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The CI/PI will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Other Ethical Considerations

Other ethical concerns are not expected to be an issue.

13.5. Reporting

The database manager shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

13.6. Transparency in Research

A lay summary of the research will be available on HRA Research Summaries.

13.7. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by anonymisation before sharing with researchers. There will be a unique participant study number once the data is extracted from the REDCap database for processing. Only the research team and the clinicians directly caring for the patient will have sufficient access to the database to re-identify patients once anonymised. Personal and identifiable data will be retained on the REDCap database itself to allow patient information to be kept updated. The database will be stored securely and only be accessible to study staff and authorised personnel. For access to anonymised data, researchers outside of this study will need to apply specifically and request the exact data they require. This, in addition to the removal of all hard identifiers and limited or no access to the database as a whole (beyond the standard access to their own patients), and anonymisation risk assessment, will minimise any possibility of reidentification. However, as these are rare diseases, the possibility of re-identification cannot always be completely eliminated. The study staff and sponsor will safeguard the privacy of participants' personal data.

For patients who consent to be contacted regarding future research, the database will only be used to identify those who meet inclusion criteria for a study. No contact details will be held for the patients in the database, and any communication with them regarding future research will be via their clinical team only. No information regarding eligible patients will be passed to other research teams by the database team.

13.8. Expenses and Benefits

No payments to participants will be required.

14. FINANCE AND INSURANCE

14.1. Funding

Funding will be fully provided by Myaware.

14.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

14.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with any third parties.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by Myaware. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

16. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

17. ARCHIVING

The database data will be stored securely on the Medical Sciences Division (MSD) REDCap servers. Furthermore, anonymised data that is downloaded as a spreadsheet for research purposes will be stored on the secure MSD network drives and back-ups created as per standard MSD IT department protocols.

The REDCap database is intended to remain active indefinitely, but at least for a minimum of 3 years. The downloaded, pseudonymised data will also be retained for a minimum of 10 years, though this may be extended depending on research needs.

18. REFERENCES

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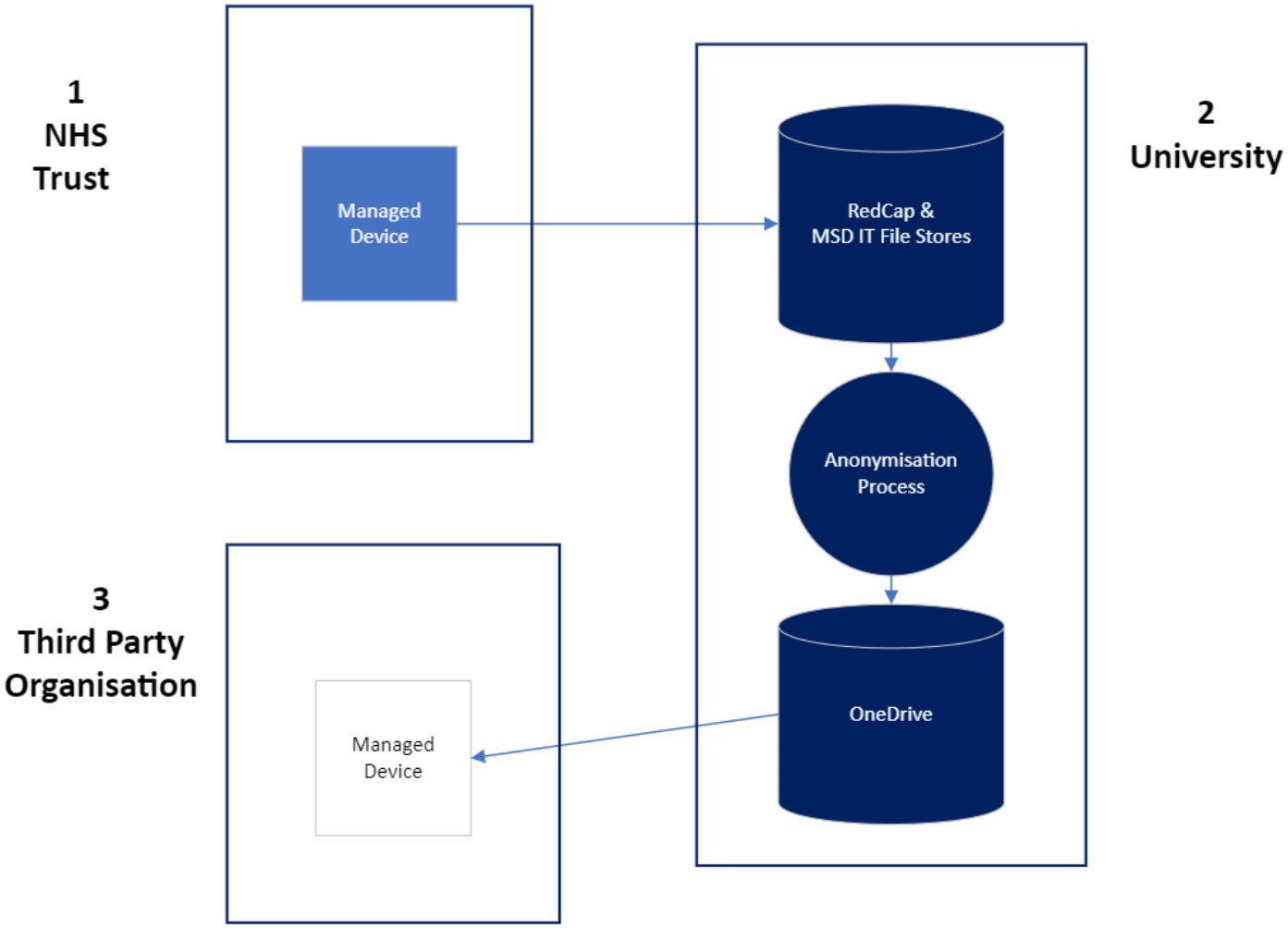
19. APPENDIX A: DATA DICTIONARY

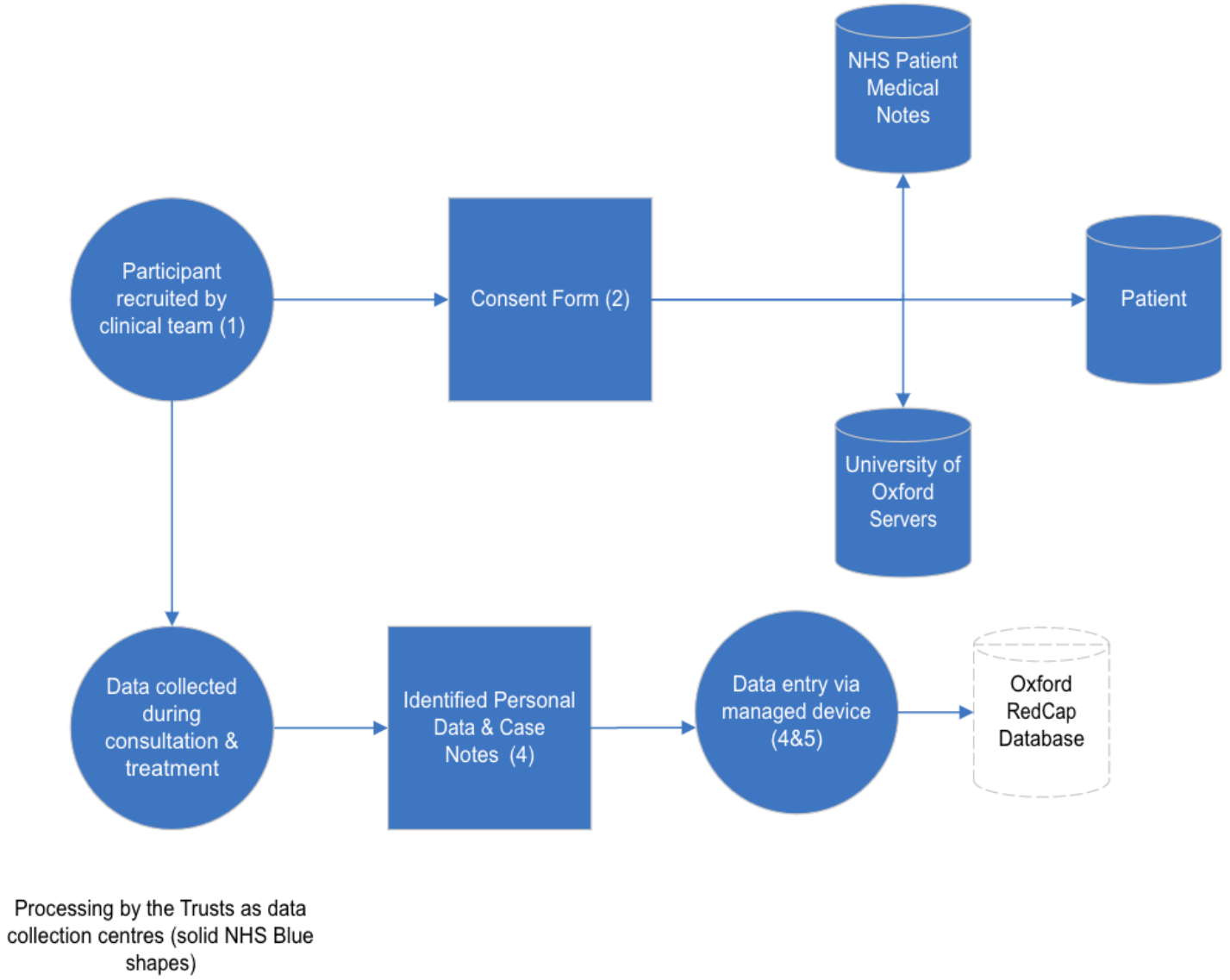
Please see separate document Data Dictionary v1.1

Appendix B – UK Myasthenia Database Dataflow

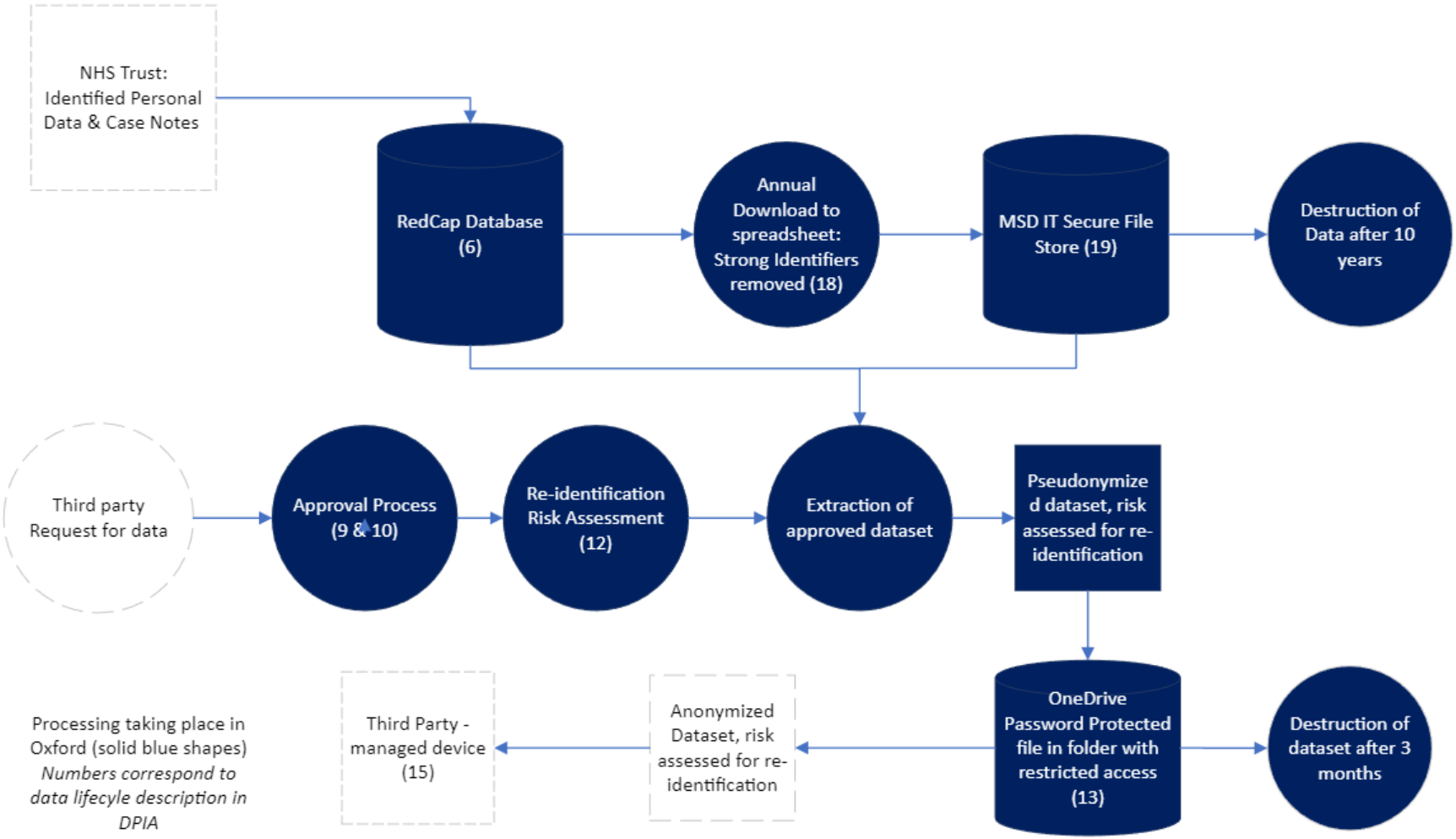
1. Overview



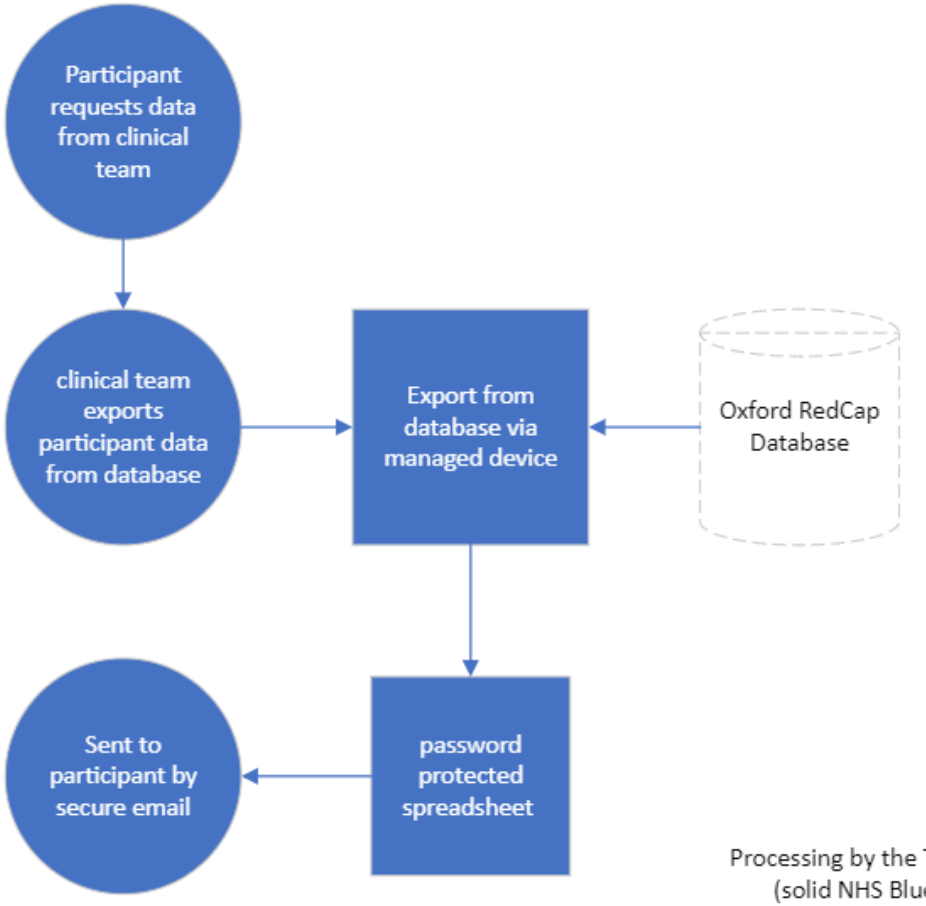
2. NHS Trust



3. University of Oxford



4. Participant Data Request



Processing by the Trust (as Site)
(solid NHS Blue shapes)
Numbers correspond to data lifecycle in DPIA

20. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	22/03/2023	M. Ashraghi	New PIs/data collection centres added. Appendix A: Data Dictionary updated to version 1.1.
2	1.2	30/06/2023	M. Ashraghi	New PIs/data collection centres added, Appendix A (Data Dictionary) updated to version 1.2, sponsor contact email updated.
3	1.3	12/10/2023	M. Ashraghi	New PI/data collection centre added.
4	1.4	20/12/23	M. Ashraghi	New PI/data collection centre added
5	1.5	28/02/2024	F.Ferguson	New PI/data collection centre added
6	1.6	27/06/2024	F.Ferguson	New PI/data collection centre added
7	1.7	29/04/2025	F.Ferguson	New PI/data collection centre added
8	1.8	15/12/2025	F. Ferguson	Database end date extension

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / HRA submission.
Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).