Full Title: **E**xploring the E**X**perience of **P**atients and Caregivers **L**iving with mit**O**chond**R**ial Stroke-Like **E**pisodes

Short Title: EXPLORE

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ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
CI	Chief Investigator
GCP	Good Clinical Practice
HRA	Health Research Authority
HSS	Highly Specialised Service
ICF	Informed Consent Form
ISF	Investigator Site File
NHS	National Health Service
PI	Principal Investigator
PICS	Participant Identification Centres
REC	Research Ethics Committee
SLE	Stroke-Like-Episodes
SOP	Standard Operating Procedure
TMF	Trial Master File
WCMR	Wellcome Centre for Mitochondrial Research

Contents

STUDY SUMMARY

Study Title	Exploring the experience of patients and caregivers living with mitochondrial stroke-like episodes
Short Title/Acronym	EXPLORE
Summary of Participant Population	Patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. This is a subgroup of patients with mitochondrial disease predominantly manifesting with seizures and progressive cognitive deficits. We will also include caregivers/family members of MELAS patients, as their views and experience provide an additional and valuable insight.
Summary of Design	This is a qualitative study consisting of: **Focus Groups** (estimated 6 sessions) involving a total of **24 - 30 participants** will be conducted. These will consist of: • Patient Focus Groups (approx. 4 or 5 participants per group)* • Caregiver/family member Focus Groups (approx. 4 or 5 participants per group) **caregivers may attend as chaperones but will not be active participants*
Planned Sample Size	**24- 30 participants** will be recruited • N = 12-15 patients with MELAS • N = 12-15 caregivers or family members of a patient with MELAS. This may also include those who have lost someone to the condition.
Proposed Overall Study Duration	12 months

Primary Objective	• Explore patients' and their caregivers' ability to recognise symptoms associated with stroke-like episodes (SLEs). • Explore the experiences of patients and their caregivers in seeking medical help when an SLE is suspected. • Explore the experiences of patients and their caregivers regarding hospital admission for a SLE/suspected SLE. • Explore if the patient has had any physical and cognitive rehabilitation following an acute admission for a SLE. • Explore the long-term impacts of SLEs on activities of daily living and quality of life in patients and their caregivers.
Secondary Objective	• Creation of a collection of data on MELAS and patient experiences of SLEs to inform future research. • Development of quantitative questions for a large-scale survey of patient and caregiver experiences of living with MELAS and seeking and accessing treatment for, and rehabilitation following, a SLE .

BACKGROUND

A stroke-like episode (SLE) is a neurological emergency experienced by a subgroup of patients living with mitochondrial disease.[1] Patients with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) can manifest various symptoms which primarily affect the central nervous system and muscles; including seizures, confusion, headaches, language difficulties and visual disturbances.[2,3] Patients often acquire new cognitive deficits and risk losing independent living following each SLE. Currently, no curative treatments are available for patients presenting with SLEs and the associated neurodegeneration.

Early recognition of SLE symptoms and initiation of anti-seizure medication is crucial to limit the extent of brain injuries related to seizures and can potentially improve outcomes following such events. European consensus based clinical guidelines on the investigation and management of SLEs are now available for medical professionals.[4] However, the experience and perspectives of patients and their caregivers, including the recognition of SLE symptoms, attendance to primary and secondary care services, and the rehabilitation after the acute presentation, have not been systematically studied.

STUDY AIM

The overall aim of the project is to increase understanding of patient and caregiver/family member experiences of mitochondrial stroke-like episodes. Understanding these experiences and exploring patient and caregiver perspectives will be integral to identifying potential barriers to accessing acute medical care, improving service provision and ultimately, patient outcomes.

We also plan to use the data collected in this study as a resource to inform the design of future research projects and in development of a questionnaire for use in future research.

OBJECTIVES

Primary Objectives:

1. Explore patients' and their caregivers' ability to recognise SLE symptoms;
2. Explore the experiences of patients and their caregivers in accessing medical help when an SLE is suspected;
3. Explore the experiences of patients and their caregivers regarding hospital admission for a SLE/suspected SLE;
4. Explore if the patient has had any physical and cognitive rehabilitation following an acute admission for a SLE;
5. Explore the long-term impacts of SLEs on activities of daily living and quality of life in patients and their caregivers.

Secondary Objectives:

1. To establish a collection of data from patients and caregivers relating to MELAS and their experiences of SLEs that can be used to inform the design of future research projects and funding applications;
2. To use the data collected to help formulate quantitative questions for inclusion in questionnaires about patient and caregiver experiences of MELAS.

STUDY DESIGN AND SETTING

The study will consist of a number of small Focus Groups (up to four or five participants per session) with patients with mitochondrial disease who have experienced SLEs, or with caregivers/family members of patients who have experienced SLEs.

Separate Focus Groups will be conducted for each participant group (patients or caregivers). Both a patient and their caregiver can participate in the study (i.e., in their separate, respective Focus Groups) however there is no restriction on a patient or caregiver participating on their own.

Twenty-four to 30 participants in total (12 to 15 mitochondrial disease participants and 12 to 15 caregivers) will be recruited.

In addition to taking part in the Focus Groups, participants will be asked to provide brief details about their (or the person they care for) demographics and relevant medical history (including genetic diagnosis).

Focus Groups will either take place in person at an accessible location within Newcastle University, or virtually (via videoconferencing software), depending on participant preference.

Potential participants will be identified by their direct clinical care teams at NHS Participant Identification Centres (PICS). These will include the Highly Specialised Service (HSS) for Rare Mitochondrial Disorders for Adults and Children based in Newcastle (Newcastle Hospitals), London (Queen Square, UCLH) and Oxford (Oxford University Hospitals NHS Foundation Trust).

Potential participants may also self-refer themselves to the study team in response to adverts on the websites of the Wellcome Centre for Mitochondrial Research, and mitochondrial disease patient organisation partners such as The Lily Foundation. The study will also be publicised via social media platforms.

ELIGIBILITY CRITERIA

Inclusion Criteria

To be eligible to participate **all participants** must:

- Be aged ≥16 years
- Have ability, in the opinion of the study team, to participate in study activities
- Be capable of providing informed consent and have capacity at the time of the focus group or interview

Patients must:

- Have a genetically confirmed diagnosis of mitochondrial disease
- Have a diagnosis of MELAS/evidence of SLEs, as confirmed by their mitochondrial specialist

Caregivers/family members must:

- Be a spouse, partner, parent(s), legal guardian, or other family member close to a patient (patient must have a confirmed diagnosis of MELAS/evidence of SLEs), either living in the same house, or in contact with the patient in a caregiver relationship

Exclusion Criteria

Participants will not be eligible to participate if:

- They lack capacity to provide informed consent or lose capacity between the time of consent and the Focus Group
- Are unable to participate in study activities, in the opinion of the study team or inappropriate to participate due to significant physical or cognitive impairment
- Are aged <16 years

RECRUITMENT AND CONSENT

Participant identification:

Via NHS Participant Identification Centres

Potential participants will be identified for the study by direct clinical care teams at NHS PICs. This will be via screening of clinic lists and also via interrogation of the Wellcome Centre for Mitochondrial Research (WCMR) Patient Cohort (MitoCohort): A Natural History Study and Patient Registry (previously known as the MRC Mitochondrial Disease Cohort) (REC Ref: 13/NE/0326). The MitoCohort is a multicentre collaboration with University College London and Oxford University Hospitals that has > 1900 registered patients with extensive storage of clinical, biochemical and genetic information. Patients registered on the MitoCohort have consented to receive information about clinical trials or research studies they may be eligible for.

Patients, or the caregivers/family members of patients, identified as potentially suitable for the study will be approached and provided with details about the study during their routine clinical appointment; via invitation letter; or via telephone call/email to ascertain interest. This will be done by members of the direct clinical care team.

Where a caregiver/family member of a patient who is deceased is known to the direct clinical care team and it is considered appropriate, the care team may forward details of the study to this caregiver. The direct care team may also forward details of the study to caregivers of patients where the patient themselves is ineligible for the study (e.g., if lacking capacity to consent) but where participation of the caregiver may still be suitable.

A Participant Information Sheet (PIS) about the study will be provided which includes contact details for the study team. Potential participants (patients or caregivers) will be asked to contact the study team directly if interested in taking part.

Via Advertisement

In addition to recruitment via PICs, the study will be publicised on a number of websites and social media channels including the Wellcome Centre for Mitochondrial Research website and via mitochondrial disease charities (e.g. The Lily Foundation).
Posters advertising the study may be displayed in clinical areas of participating PICs and the study may be publicised at public and patient facing events and conferences.

Any study advertisement will advise patients/caregivers who are interested in participating to contact the study team directly.

Potential participants recruited outside of NHS PICs will be asked to provide evidence of mitochondrial disease with SLEs, in order to verify their eligibility for the study. It is anticipated that this will be confirmed by allowing a member of the study team to see a piece of recent, relevant, clinical correspondence. Such correspondence will be viewed by the study team to confirm the diagnosis / evidence of SLEs, however will not be stored or used for purposes other than verifying eligibility.

Participant Consent:

Potential participants who contact the study team will be provided with the opportunity to discuss the study in more detail and to have any questions answered. They will be allowed as much time as they require to decide whether to take part.

Following this, an appointment to attend a Focus Group (either in person or via videoconference) will be arranged.

Participants will be asked to provide informed consent for the study ahead of any Focus Group.

This will involve completing an informed consent form (which can be returned in person, or via post/email). Upon receipt, the form will be reviewed and countersigned by a member of the research team. A copy of the fully completed consent form will be returned to the participant (either in person, or via post/email) for their records. The study team will retain the original form.

Participants will be advised that they can withdraw from the study at any point before the focus group. It will be explained that they can also withdraw after this (i.e., during the Focus Group), however that it may not be possible to remove any data already collected, or used.

Loss of Capacity

It is not anticipated that any recruited participants will lose capacity between the time of consent and participation in a Focus Group. However, in the unlikely case that this occurs, the participant would be removed from the study. Depending upon timing and the number of participants recruited (e.g. if still waiting to hit the minimum recruitment target of 24), the participant may be replaced. However, if the minimum recruitment target has already been reached, the participant will not necessarily be replaced.
Participants will be advised during recruitment and consent that if they are withdrawn for any reason, their data collected up until the point of withdrawal will be retained.

STUDY PROCEDURES

Screening/Confirmation of Eligibility

Medical history of potential participants (to verify that they satisfy the inclusion criteria and do not meet any exclusion criteria) will be reviewed prior to approach via NHS PICS.

Where potential participants refer themselves, this will be verified during discussion with the participant and may require sight of recent clinical correspondence (as outlined above).

We will apply purposive sampling to invite eligible participants for focus group using specific criteria (**Table 1**) to ensure the expressed views are representative of patients and caregivers living with MELAS syndrome. The Principal Investigator or another appropriately delegated member of the research team (e.g. sub-investigator, research nurse or research physiologist) will be responsible for confirming final eligibility for participation.

Patient participant	**Caregiver participant**
≥1 female participant with MELAS	≥1 male participant
≥1 participant presenting with stroke-like episode after the age of 40 years	≥1 participant that currently holds a full-time or part-time employment
≥1 participant presenting with stroke-like episode between the age of 16 to 40 years	

Table 1. Suggested Purposive sampling criteria for Focus Group interviews

(NOTE: These criteria are suggested only and may be reviewed/adjusted depending on the progress of recruitment)

Collection of SLE History and Demographic Data

As part of focus group preparation, the following data items will be collected from participants:

- Age (of patient)
- Sex of patient (at birth)
- Mitochondrial disease genotype
- Ethnicity of patient
- Age at first SLE*
- Age at most recent SLE*
- Estimated number of SLEs experienced to date*
- Whether the patient participant is the proband with MELAS syndrome in the family

**These details may be available via the MitoCohort database (hosted by Newcastle University). If the participant/caregiver is unsure of any details, and these details are available from the MitoCohort, they will be requested from the MitoCohort (with participant consent). An application to the MitoCohort Oversight Committee for access to the data will be made.*

Schedule of Events

		Patients *	**Caregivers ****
Study Assessment	Screening & Informed Consent	All	All
Eligibility Confirmation *(if applicable)*	X		
Informed Consent	X		
Focus Groups*, **		X 3 Focus Groups: Group 1: N = 4-5 Group 2: N = 4-5 Group 3: N = 4- 5	X 2 Focus Groups: Group 4: N = 4-5 Group 5: N = 4-5 Group 6: N = 4- 5

** caregivers may accompany the patient (i.e., as a chaperone for support only/ not as an active participant).*

*** caregivers involved as a patient chaperone are not obligated to participate in the caregiver Focus Group*

Focus Groups

Approximately **six** Focus Groups, with the number of participants limited to **four or five per group** will be conducted.

The anticipated composition of these groups will be as follows*:

- **Group 1 –** Patients (N=4 or 5); face-to-face
- **Group 2 –** Patients (N=4 or 5); virtual
- **Group 3 –** Patients (N=4 or 5) face-to-face or virtual
- **Group 4 –** Caregivers (N=4 or 5); face-to-face
- **Group 5 –** Caregivers (N=4 or 5); virtual
- **Group 6 –** Caregivers (N=4 or 5); face-to-face or virtual

**Depending upon participant preference or scheduling, it is possible that the number or format (e.g. face to face or virtual) of Focus Groups may change from the above.*

Location and Format of Focus Groups

Face-to-face Focus Groups will take place in an accessible, quiet room located within Newcastle University. The room will be chosen and set-up to enable patients and caregivers to feel comfortable participating in open discussions.

Virtual groups will take place via Newcastle University approved video-conferencing software (e.g., MS Teams or Zoom). Participants will be asked to ensure that they have somewhere private and comfortable to dial in from. They will also be provided with instructions and guidance on logging into the system and using the relevant features.

Each Focus Group is anticipated to last up to 180 minutes (3 hours). Regular breaks will be scheduled to avoid fatigue. At the in-person groups, refreshments and lunch will be provided. Focus Group etiquette and safeguarding will be covered prior to the start of the discussions and participants will be asked to keep the content of the discussions confidential.

At least one moderator (or facilitator) and one assistant (and note taker) will facilitate each Focus Group. The moderator will use a Semi-Structured Moderator Interview Guide (**Appendix 1**).

Post-Study Activities

Following completion of the Focus Group, study participation for each participant will end.

Participants will be invited to provide feedback on the study via a survey, which can be completed on paper or online. The survey is optional and will be anonymous.

Participants will also be asked whether they would like to be involved in future projects, including in the development and testing of a future patient questionnaire on SLEs. Contact details for participants who have agreed to have future involvement will be stored by the study team for this purpose.

Withdrawal Criteria

Participants have the right to withdraw from the study at any time without having to give a reason. Participants who withdraw from the study will be advised that the data provided up to the point of their withdrawal will be retained.

The Principal Investigator or another member of the study team may stop a Focus Group at any time or may discontinue a participant from the study if considered necessary for any reason. This may include in the event of participant distress, following a disclosure that requires immediate action, or in instances of unacceptable behaviour during the session.

The reason for any investigator-initiated withdrawal will be discussed with the participant.

End of Study

The end of study for each participant will be completion of their Focus Group participation.

The overall end of study will be defined as completion of the last participant Focus Group. However, transcription of recordings and data analyses may continue for up to 12 months following the end of study.

STATISTICS

Quantitative Analyses

Descriptive statistics will be used to analyse the demographic characteristics of the patient and caregiver participants. The Focus Groups will provide an opportunity to gather insight into particular topics. These findings will be investigated for themes and ideas for future quantitative approaches, however, will not be interpreted for statistically significant results in the current study.

Qualitative Analyses

We estimate that at least three Focus Groups per category are required to reach data saturation according to the literature[5,6]. Two independent investigators will apply a pre-specified analytical network similar to the methodology described[7] for coding and organising these codes into different themes using NVivo software[8] (**Appendix 2**).

MONITORING, AUDIT & INSPECTION

The study may be subject to audit or monitoring by representatives of the Sponsor (or their delegates). Each member of the study team will permit study-related monitoring, audits and regulatory inspection including access to all essential documents and data relating to the study. The study team will follow GCP and will adhere to all local regulatory and quality assurance practices.

RISKS & MANAGEMENT OF ISSUES

This is a non-interventional study that does not involve any procedures with participants. As such, study related adverse events are not anticipated and will not be recorded.

Focus Groups

The study involves discussion of topics that may be highly emotive for participants. They will be asked to reflect on their or their family members, condition, prognosis and care. Due to the severe nature of this condition and the lack of current effective treatments, this may result in sensitive and difficult issues being raised.

Potential participants will be advised as part of the recruitment process that potentially emotive issues will be discussed. They will be provided with Focus Group schedules in advance of the sessions so that they are aware of the topics that will be raised and can make an informed decision on whether or not they would like to take part.

The Focus Group schedule (Semi-Structured Moderator Interview Guide) has been designed in collaboration with mitochondrial disease clinicians who work with the Highly Specialised Mitochondrial Service. This is to ensure that the questions are relevant and posed in a manner and sequence most appropriate to the topic and sensitivities of participants.

Members of the research team may already be known to participants and may be involved in their clinical care, however in order to ensure that participants feel free to discuss their treatment, sessions will be moderated by a member of the team who is not directly involved in the participants care. Moderators will also be experienced in facilitating focus group discussions in this area.

Participants will be provided with guidance on ‘Focus Group etiquette’ in advance of the sessions. This includes highlighting the need for discussions to be kept confidential and to have respect for the views of other participants. Participants will also be advised that additional support is available following the session should they need it and will be signposted to relevant support services.

If any issues are raised during the session which are of concern to the moderator (e.g., potential criminal disclosures, safeguarding or clinical issues), or if a participant requests additional support, this will immediately be escalated to the Chief/Principal Investigator (who is a clinical academic/honorary NHS consultant neurologist, specialising in mitochondrial disease). The Chief/Principal Investigator will then liaise with the participant, and their clinical care team, and with any relevant authorities, to ensure that the appropriate clinical or psychological support is accessed and/or the appropriate action is taken.

Participants will be advised in advance of the sessions of the potential need to make onward referrals should a disclosure requiring action be made.

The study team may also request consent to contact participants following the session to ‘check-in’ with them if any concerns are noted.

Details of any issues raised, or any referrals made, as part of the study will be logged within the study Trial Master File (in a pseudo-anonymised) format.

As fatigue is a very common symptom in mitochondrial disease, this will be taken into account during the scheduling and conduct of Focus Groups. Ample time for discussions will be allowed and regular breaks will be scheduled. For participants who attend for in-person Focus Groups- refreshments including lunch will be provided. Travel and accommodation, if required, will also be arranged.

Data

Data collected and processed as part of the study will be secured and managed as outlined in the data management section below. Participants will be advised that recordings of the Focus Groups (audio and video) will be made and that this will include identifiable information (especially in the case of video). They will be asked to provide explicit consent for this. Any incidents relating to processing, storage or sharing of data are not foreseen, however should these occur, they will be reported to Sponsor and managed as per the Newcastle University Research Data Management Policy.

ETHICAL AND REGULATORY CONSIDERATIONS

Regulatory Compliance and Research Ethics Committee Review and Reports

The study will be conducted in accordance with GCP. The Chief Investigator (also the Principal Investigator) will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the study. All parties will conduct the study in accordance with this ethical opinion.

An agreement between Sponsor and each participating NHS PIC will be put in place, and confirmation from each PIC of agreement to their activity, will also be obtained prior to the start of recruitment via this method.

An annual progress report will be submitted each year to the REC by the CI until the end of the study. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The CI will notify the REC of the early termination or end of study in accordance with the required timelines.

Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI and Sponsor. Substantial amendments will be submitted to the REC and HRA and will not be implemented until approvals from both are in place. Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the study; or
b) the scientific value of the study

The sponsor must be notified immediately of any incident that may be classified as a serious breach.

The Chief Investigator will also, on behalf of Sponsor, notify the NHS REC within the required timelines (7 days of awareness of the serious breach).

Data Management

Source Data

Source data for this study will consist of recorded Focus Groups (audio and video files), the transcripts from these, and paper worksheets recording demographic details and medical history.

Focus Group: Access, Recordings and Transcription

Focus Groups will be recorded via computer video-conferencing software (e.g., MS Teams or Zoom) or using a digital recording device.

Access to the virtual meetings will be controlled via password or secure link that will be provided to participants via email.

Any video-conferencing software will be used under a Newcastle University licence. The recordings will be stored via the video-conferencing system in a secure area of the system, accessible to authorised Newcastle University staff only. Audio recordings from in-person sessions will be downloaded from the recording device directly onto a restricted access shared drive on Newcastle University servers accessible only to the research team.

In order to protect confidentially as much as possible, during Focus Groups, participants will be referred to by first name only.

Recordings will be transcribed as soon as possible after the session. Transcriptions will be made by an authorised member of the study team at Newcastle University. During transcription of recordings, all names will be removed and participants will be referred to by unique study ID.

Names of any hospitals and clinicians will also be removed, however these may be coded by institution type e.g. primary care provider, secondary or tertiary care service.

Transcriptions will be stored on a secure shared drive on Newcastle University servers which is accessible to the study team only.

All recordings will be deleted following transcription. A separate Data Protection SOP for the study outlines the security arrangements for the storage and management of Focus Group recordings and transcripts and study data.

Collection of Demographic and Medical History Data

Participants will be asked to provide limited demographic and medical history details (including details of genetic diagnosis). This will be recorded on paper worksheets (completed by the participant or a member of the study team during discussion with them). Completed worksheets will be returned to the study team in person or via email, however will be de-identified (referring to the participant by a unique study ID rather than by name). Completed worksheets will be held in the combined study Trial Master File/Investigator Site File (TMF/ISF) on paper and in a secure study shared drive on Newcastle University servers.

Identifiable data: Consent Forms, Study Enrolment Logs and Participant Contact Details

A number of pieces of identifiable data will be collected and stored. However, these details will not be used in the analysis or dissemination of study results and will not be shared outside the research team.

Completed study consent forms will be held in the combined TMF/ISF. This will be securely stored in the clinical trials office within the Wellcome Centre for Mitochondrial Research, Newcastle University.

An enrolment log recording the names of all study participants and linking participant name to each participant’s unique study ID will also be held in the TMF/ISF.

A list of preferred participant contact details (e.g. containing participant name, email address, postal address (if required) and telephone number) will also be retained in the TMF/ISF.

These identifiable details will be used to arrange focus group/interview appointments, to arrange travel and payment of expenses, and to provide any relevant updates to participants during the study.

Evaluation Data

At the end of their participation participants will be invited to provide feedback on their experienced of being involved in the study. This will be via completion of a survey (either online or on paper). The survey will be optional and will be anonymous (participants will not be required to provide their name or study ID). Evaluation data will be stored on paper in the TMF/ISF or online via Newcastle University Servers.

Data Handling and Governance

The study will comply with all relevant data protection legislation. A Data Protection Impact Assessment (DPIA) will be completed and approved by the Sponsor and Data Controller (Newcastle University) prior to the start of data collection.

Study data (from worksheets and from Focus Group transcription) will be collated by a member of the research team at Newcastle University. It is anticipated that Excel or a similar programme will be used to hold collated data for analysis (which will be retained in a secure area on Newcastle University servers). Only members of the study team will have direct access to the data, as approved by the study Chief Investigator. For analyses, participants will be identified via their study ID, no direct personal identifiers will be used.

Upon completion of the study and all analyses, the TMF/ISF, and associated electronic study documentation will be archived in accordance with Newcastle University procedures for a minimum of 10 years (as per the Newcastle University Research Data Management Policy Principles & Code of Good Practice).

Access to Data and Data Sharing

Direct access to study data including source data contained on Newcastle University servers and personal identifiable data contained in the TMF/ISF will be granted to authorised representatives of the Sponsor or regulatory authorities for the purposes of monitoring, audit or inspection. Consent for this will be obtained from participants during recruitment.

Following completion of the study, pseudo-anonymised sets of data may be made available for 3rd party research purposes with the appropriate data transfer procedures. Consent for this will be obtained from all participants.

Insurance and Indemnity

Newcastle University has in place a Public Liability Policy which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design, management or conduct of the study. No arrangements for cover for non-negligent harm will be included.

Participant Reimbursement for Time

In recognition that participants will be required to give up their time for participating, they will be offered reimbursement in the form of a voucher. This will recognise the time involved in preparing for, attending the Focus Group and for any evaluation activities following the Focus Group.

COMMUNICATION AND DISSEMINATION OF RESULTS

Findings from the study may be reported at local, national and international meetings, on social media platforms (including [but not limited to, Newcastle University, Wellcome Centre for Mitochondrial Research, charity partners], as well as in peer-reviewed journals. Study participants will be advised in the Participant Information Sheet that they can contact the study team to request a lay summary of the overall research results once the study is complete.

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APPENDIX 1: SEMI-STRUCTURED MODERATOR INTERVIEW GUIDE

1. Experience leading to the point of diagnosis of mitochondrial disease.

Life before the diagnosis of mitochondrial disease:

- Had you/the person you care(d) for ever heard of mitochondrial disease? (did you know it was a genetic disorder; were you aware that you had a family history)?

Symptoms before presentation of stroke-like episode:

- Did you/the person you care(d) for have any symptoms associated with mitochondrial disease (e.g. deafness, diabetes, muscle weakness) prior to the first occurrence of an acute stroke-like episode?

- Were you informed about the risk and symptoms associated with stroke-like episodes by the medical professionals? *(this question is applicable only for those individuals who already had a genetic diagnosis of mitochondrial disease before developing stroke-like episodes)*

2. Experience leading to the acute presentation of stroke-like episode.

Diagnosis:

- How did you find the process of reaching the diagnosis of stroke-like episode?

- Did you feel that you were provided sufficient information about stroke-like episodes by the medical professionals (e.g. GP, hospital specialist, allied health personnel)?

- Following your diagnosis of stroke-like episodes (or that of the person you care(d) for), have you tried to obtain more information? (i.e. experience from other family member(s) similarly affected, published medical literature, patient organisation/s, social media/ patient forum or other sources)?

- If you/the person you care(d) for were to have a further hospital admission for a suspected stroke-like episode, do you feel confident to recognise the relevant symptoms?

Management:

- Reflecting on your most recent admission with stroke-like episode/s (or that of the person you care(d) for), what was the length of stay in hospital? Did you feel that the hospital team understand the condition?

- Reflecting on your most recent admission with stroke-like episode/s (or that of the person you care(d) for), what treatments have you been offered? (anti-epileptic drugs, L-arginine and other)

- Reflecting on your most recent admission with stroke-like episode/s (or that of the person you care(d) for), how would you describe the overall experience?

3. Experience leading to post-acute event.

Rehabilitation:

- After you/the person you care(d) for has been discharged from hospital, do you feel you received appropriate rehabilitation and support in the community?

- Have you or the person you care(d) for ever been admitted to a respite care facility? If so, what was the length of stay?

Follow up arrangement:

- In general, how well do you feel that you are supported by your local clinical services (e.g. general practitioners, general neurologist, clinical geneticist, physiotherapist) following the discharge from the hospital and/or rehabilitation service?

- Have you attended one of the Highly Specialised Service for rare mitochondrial disorders (Newcastle, London and Oxford)? What has been your experience?

4. Impact of stroke-like episodes on various aspects of life.

Seizures

- How do you/the person you care(d) find living with seizures following stroke-like episodes?

- How do you/the person you care(d) find taking anti-epileptic medications?

Cognitive:

- Have you/the person you care(d) for suffered from persistent/progressive cognitive impairment (e.g. reduced concentration span, short-term memory deficits, difficulties to perform visual-spatial tasks, language deficits)? What are the impacts on the activities of daily living?

Physical impact:

- Have you/the person you care(d) for experienced physical symptoms (e.g. muscle weakness, fatigue) following the stroke-like episodes? What are the impacts on the activities of daily living?

Psychological impact:

- What do you feel is the psychological impact you/the person you care(d) for following stroke-like episode(s)?

Impact on relationships:

- As a result of mitochondrial stroke-like episodes, has the relationship between you/the person you care(d) for, changed (for example, with family, parents, partners, siblings, children; friends, acquaintances or strangers)?

Impact on work/studies:

- Have you/the person you care(d) for had to adjust your work or study as a result of mitochondrial stroke-like episodes (for example, reduced professional commitments, stopped working or education)?

Impact on recreation:

- Have you/the person you care(d) for had a change in the type or time spent in recreational activities as a result of mitochondrial stroke-like episodes? (for example, given up hobbies).

Financial impact:

- As a result of mitochondrial stroke-like episodes, have you/the person you care(d) for faced financial challenges as a result? (for example, loss or reduction of personal income due to employment circumstances/reduced job activity; purchase of medications or additional out of pocket expenses).

- Have you/the person you care(d) for encountered any difficulties navigating the social welfare system?

5. Other

- What aspects of care/support would you/ the person you care(d) for like to receive going forwards?

APPENDIX 2: ANALYTICAL FRAMEWORK FOR CODING FOCUS GROUP INTERVIEWS

Adapted from Chen et al.

SECTION	THEMES	CODES
Experience leading to the point of diagnosis of mitochondrial disease	Life before the diagnosis of mitochondrial disease	• Identity/role • Employment/education • Activities of daily living • Hopes, dreams and plans • Awareness of mitochondrial disease • Personal risk of mitochondrial disease (genetic inheritance)
	Symptoms before presentation of stroke-like episode	• Neurological symptoms • Non-neurological symptoms • Significance/meaning of symptom • Emotional response to stroke-like episodes
Experience leading to the acute presentation of stroke-like episode	Diagnosis	• Recognition of symptoms associated with stroke-like episode • Contact with the primary care service • Contact with the hospital service • Investigations/tests • Number of providers • Information about stroke-like episodes • Emotions/feelings about diagnostic process
	Management	• Alert card/emergency care plan • Treatments (anti-epileptic drugs) • Use of L-arginine • Use of any other treatments • Experience of hospital stay • Emotions/feelings about treatments received
Experience leading to the post-acute event	Rehabilitation	• Physical rehabilitation (e.g. weakness) • Language • Visual function • Emotions/feelings about rehabilitation (or lack of)
	Follow up arrangement	• Local service (neurology/clinical genetics) • Highly Specialised Service for Rare Mitochondrial Disorders

SECTION	THEMES	CODES
Impact of stroke-like episodes on various aspects of life	Seizures	• Severity • Emotions/feelings about seizures • Issues related to driving
	Cognitive	• Memory • Language • Visual-spatial navigation • Emotions/feelings about cognitive impact • Strategies/management
	Physical impact	• Symptom • Emotions/feelings about physical impact • Strategies/management
	Psychological impact	• Anxiety • Depression • Strategies/management
	Impact on relationships	• Interactions with parents • Interactions with children • Interactions with partner • Interactions with friends and colleagues • Interactions with strangers • Emotions/feelings about relationships • Strategies/management
	Impact on work/studies	• Time off work • Change in duties/routine • Unemployment • Emotions/feelings about changes to work • Strategies/management
	Impact on recreation	• Physical activities • Social activities • Emotions/feelings about recreation • Strategies/management
	Financial impact	• Related to change in work/employment • Related to medication/treatment • Other expenditure • Social security/welfare/benefit • Emotions/feelings about financial impact