Non-CTIMP Study Protocol

Evaluation of Sleep in SYNGAP1

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CONTENTS

LIST OF ABBREVIATIONS

Insert abbreviations as required

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
ASD	Autism Spectrum Disorder
CI	Chief Investigator
CRF	Case Report Form
ECG	Electrocardiography
EEG	Electroencephalography
EMG	Electromyography
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ID	Intellectual Disability
NREM	Non-rapid eye movement
PI	Principal Investigator
PSG	Polysomnography
QA	Quality Assurance
REC	Research Ethics Committee
REM	Rapid eye movement
SOP	Standard Operating Procedure
SpO2	Oxygen saturation

1 INTRODUCTION

1.1 BACKGROUND

Sleep is essential for a healthy development and people with Intellectual Disability (ID) and Autism Spectrum Disorder (ASD) are more likely to suffer from disordered sleep than the general population (1). Disordered sleep results in deficits in cognition, memory, behaviour, emotional functioning and quality of life (2). Therefore understanding disrupted sleep patterns in people with ID and ASD who already face social and behavioural challenges is important in order to develop effective treatment strategies in this population.

This study will take a translational perspective to investigate the sleep patterns and 24 hour circadian rhythms of people with SYNGAP1-related intellectual disability, a currently untreatable genetic condition strongly associated with ID, ASD and epilepsy (3–6). SYNGAP1-related ID is believed to account for approximately 0.5 to 1% of cases of ID and severe epilepsy (7,8). Hence it is prevalent in these populations and merits further study. The prevalence of sleep problems in SYNGAP1-related ID ranges from 61.8% to 100% of participants in published studies (3,5,6). Preliminary work from our research group has identified sleep problems in all thirteen individuals in whom parental report data was gathered using the Children's Sleep Habits Questionnaire (developed by Owens in 2000). Although it is clear that poor sleep is a significant issue for those with SYNGAP1-related ID, the nature of sleep patterns and circadian rhythm (sleep-wake cycle) in affected individuals is yet to be systematically evaluated.

In tandem with our data from human participants, we are working in collaboration with neuroscience colleagues who have collected preliminary sleep data from *Syngap*$^{+/\Delta Gap}$ rats. These are heterozygous rodents with a mutation in the *Syngap1* gene. This means they have one normal copy of the *Syngap1* gene and one mutated copy. The mutated copy has a large deletion in it including a region called the GAP domain which is believed to be essential for the normal function of the Syngap protein which the gene codes for. These preliminary sleep recordings using EEG to measure electrical activity in the rat brains have identified absence seizures around sleep onset. They have also found changes in sleep architecture such as reduced transitions between sleep states and more time in wakefulness in *Syngap*$^{+/\Delta Gap}$ rats compared to wild type rats which don't have mutations in *Syngap1*. Coupled with results from studies in people with SYNGAP1-related ID and mouse models of the condition which identified increased epileptiform (seizure-like) activity on EEG at sleep onset and during sleep (5,10), this suggests there may be similarities in sleep-related EEG data across species.

In this study we will therefore collect prospective sleep data from participants with SYNGAP1-related ID and compare it to the patterns found by our collaborators in the *Syngap*$^{+/\Delta Gap}$ rats. As sleep disorders can include circadian rhythm disturbance, we will also record data pertaining to this. This is something our collaborators are also now exploring in the rats. Circadian rhythm is the daily natural, internal process

which repeats on each rotation of the Earth (roughly every 24 hours). It is linked to the regulation and function of many biological processes such as sleep-wake cycle, hormone production and core body temperature. When disrupted, it can impact on daily activities and physical and mental health (see reviews by Kecklund, 2016; Hou, 2020). This demonstrates why analysing the sleep-wake aspects of circadian rhythm is important.

We hope this study will lead to the identification of sleep and circadian rhythm biomarkers which could in future be used as markers of treatment response in trials of potential therapeutics.

1.2 RATIONALE FOR STUDY

Our primary research question is whether the differences in brain electrical activity in rats with *Syngap1* mutations during sleep are also present in people with SYNGAP1-related ID. Using EEG which can be done in both species will allow direct comparison with the rodent research and hence we hope to identify biomarkers in the sleep patterns of rats and people with *SYNGAP1* variants which can in future be used as markers of treatment response.

The recognised gold standard method of investigating sleep in people is polysomnography (PSG) which measures multiple parameters including video recordings of body movements and sleep-related behaviour, eye and muscle movements, oxygen levels, respiratory (breathing) effort and heart function in addition to EEG recordings. We propose to use a simplified form of PSG in participants' homes. This will facilitate the identification not only of potential biomarkers, but also of any seizure activity, sleep-disordered breathing and parasomnias which are medical conditions that can disrupt sleep (13). Sleep-related seizures can increase the risk of Sudden Death in Epilepsy (SUDEP) (14). Given the known link between SYNGAP1-related ID and epilepsy (3–6) they are very important to identify.

PSG is typically conducted in a sleep laboratory with a plethora of equipment and is costly and potentially less practicable than other methods (15). For people with ID and ASD new experiences and unfamiliar environments can cause significant distress even without undergoing evaluation in a sleep laboratory. Stress can increase the likelihood of seizures, leading potentially to significant challenges in obtaining representative sleep data in participants with SYNGAP1-related ID. We therefore aim to analyse sleep patterns and also circadian rhythm in a less distressing manner by minimising the equipment involved and recording in participants' own homes. We anticipate this will reduce any risk to participants' mental state (anxiety in particular) and physical health (e.g. seizures). Similar methodology was successfully utilised in people with Down Syndrome, another condition associated with ID and sometimes ASD (16).

<u>Benefits of participation in this study</u>

Although sleep problems are known to be prevalent in people with SYNGAP1-related ID, the nature of these has not yet been delineated. Hence the most immediately tangible benefit to each individual participant in this study will be gaining a better

understanding of their sleep patterns including the ability to identify specific clinical sleep disorders, sleep-related seizures and circadian rhythm disorders which may require further investigation and treatment. As noted, ongoing seizure activity, particularly when it is sleep-related can result in sudden death, hence the identification of this is extremely important (17). Furthermore, as sleep disruption and circadian rhythm disorders can result in deficits in cognition, memory, behaviour, emotional functioning and quality of life (2,11,12), being able to address such conditions may improve various areas of participants' lives. This is all the more important for people with SYNGAP1-related ID who already face daily challenges due to their intellectual disability, likely epilepsy and potentially associated ASD and multiple physical health problems.
The data will be scanned as soon as possible following the recordings so that any seizures or other easily identifiable sleep problems that may need treatment will be noted as soon as possible. The research team will inform the participant and their parent/Guardian and will also write directly to the participant's General Practitioner and any relevant secondary care specialist the participant is under the care of e.g. a neurologist. The participant/parent/Guardian will provide the information of the doctor(s) they wish the information to be sent to. The initial letter will explain that early data analysis has indicated a likelihood of seizures (or other relevant clinical information). A second letter will be sent once the data has been fully analysed to provide as much clinically relevant information as possible. Contact details for the study team will be included should the doctor(s) wish to discuss the findings further. This is made clear in the study Participant Information Sheets and Consent Forms. Although at present there is no specific treatment for SYNGAP1-related ID, trials of therapeutics in rodents with *Syngap1* mutations are in progress and many have used existing human medications which have been repurposed. Repurposed medications are likely to be approved quicker by licencing authorities as they are already known to be safe. By taking part in this study, participants will directly assist with the search for biomarkers of this condition which can be used to facilitate this development of therapeutics for SYNGAP1-related ID.

As the control participants will be siblings or close associates of people with SYNGAP1-related ID, it is anticipated that they will welcome the opportunity to help the affected person.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

Can the study of sleep and circadian rhythm in SYNGAP1-related ID identify biomarkers that can be used in future experimental medicine and clinical trials?

2.1.2 Secondary Objectives

1. Are the sleep-related seizures and differences in sleep architecture identified in preliminary *Syngap* rat data also present in people with SYNGAP1-related intellectual disability?

2. Do the participants have diagnosable sleep or circadian rhythm disorders?

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The profile of sleep patterns in people with SYNGAP1-related ID including sleep architecture and circadian rhythm data.

2.2.2 Secondary Endpoints

- Completion of non-validated medical history questionnaires
- Completion of the Children's Sleep Habits Questionnaire
- Completion of the Pediatric Quality of Life Inventory questionnaire
- Completion of a sleep diary
- Diagnosis of sleep or circadian rhythm disorders
- Diagnosis of nocturnal seizures

There is also an element of assessing the feasibility of conducting such a study in a population of people with typically severe intellectual disabilities who may struggle to tolerate some or all of the recording equipment.

3 STUDY DESIGN

This is a case-control observational study lasting 15 months. Sleep patterns of participants with SYNGAP1-related ID and unaffected controls (typically siblings) will be measured in their own homes.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We will recruit 15 people with SYNGAP1-related ID and approximately 15 controls from across the UK. No exclusions will be made on the basis of sex/gender.

4.2 INCLUSION CRITERIA

Participants must

1. Have a confirmed *SYNGAP1* gene variant
2. Be 15 years of age or younger
3. Live in the UK (Scotland, England, Wales or Northern Ireland)

4. Be able to consent to participation themselves or have a parent or someone with parental responsibility to consent on their behalf

5. Have a Study Partner who can complete questionnaires about them

4.3 EXCLUSION CRITERIA

1. Living outwith the UK

2. Lacking capacity to consent to participation themselves and lacking a parent or someone with parental responsibility to consent on their behalf

3. Aged 16 years or over

4. Lacking a Study Partner who can complete questionnaires

4.4 CO-ENROLMENT

Participants or those giving consent on their behalf will be asked for permission to retain their contact details for the purpose of re-contacting them about this study or to provide them with information about new studies they may be interested in.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

1) Patrick Wild Centre contacts list

The Chief Investigator of the study (Dr Lindsay Mizen) is a Senior Clinical Researcher at the University of Edinburgh's Patrick Wild Centre which conducts research into Autism, Fragile X Syndrome and Intellectual Disabilities. The Patrick Wild Centre has a GDPR compliant contact list which consists of people who have given explicit consent to receive updates from the Patrick Wild Centre, including details of research projects that are recruiting. The individuals on this list have not been recruited through NHS sources, they have usually signed up through our website or at events. An email or letter describing the study will be sent to individuals on this list, with a link to more details on the website along with contact details for the research team if they would like further information about the project.

2) Patrick Wild Centre website

A page will be created on the Patrick Wild Centre website with a brief outline of the study. Contact details will be provided for individuals to get in touch to request more information about the study.

3) Patrick Wild Centre social media

Information about the study will be circulated through social media, with a link to the main website page referred to above.

4) Voluntary sector organisations
Appropriate voluntary sector organisations will be contacted and asked to pass information on to their membership. These will include 'gene-specific' organisations, such as Bridge the Gap, SYNGAP Education and Research Foundation and the SynGAP Research Fund as well as those which support people with genetic or developmental disorders more generally, such as UNIQUE. Provided they are in agreement, the study leaflet will be provided to these organisations to circulate.

The participants will not be recruited through the NHS.

5.2 CONSENTING PARTICIPANTS

Potential participants will be asked for evidence of SYNGAP1-related intellectual disability diagnosis prior to consent being sought. There will be no diagnostic testing as part of this study. The study team will not seek this information from any other channels including NHS systems.

Participants will all have been provided with an information sheet tailored as far as possible to their cognitive and communication level at least 24 hours prior to meeting to discuss consent. The opportunity will be given to ask questions of the researcher.

The study is not limited by whether or not the young people recruited have the capacity to give consent. All individuals will therefore require careful assessment as to whether they have capacity to give consent. This assessment will be conducted by a clinical psychiatrist or a psychologist who will have received training in assessing capacity to give consent, either through their clinical training and / or through attendance at an appropriate course, such as that run by the Wellcome Trust Clinical Research Facility in Edinburgh. When the participant is not capable of giving fully informed consent, consent will be sought from a parent or someone with parental responsibility. The same capacity assessment will take place for control subjects.

Assessments of capacity and the process of informed consent may take place by video-link using University of Edinburgh approved software/platforms. If there is any ambiguity around the participant's capacity then a face-to-face appointment will be required before the participant or their representative can give informed consent. Participants will be able to either sign and return by post informed consent forms, or electronically consent via Adobe Sign.

A variety of information sheets and consent / assent forms will be used, depending on the participant's capacity to understand information and give consent. Communication aids will be used to maximise the understanding of those with low verbal abilities as appropriate.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form if possible. If a participant withdraws the data they have provided up to that point will continue to be used, although their identifiable information will be destroyed, such that they would become anonymised, as opposed to linked-anonymised.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

The assessments to be carried out are as follows:

A standardised clinical history questionnaire will be made available to participants once written informed consent is obtained and they or someone who knows them well will be able to complete and return it to the research team either in person or using a stamped addressed envelope that will be provided. It includes information about developmental history, medical problems and behaviour. The estimated time for completion is 20 minutes and researcher support will be available in person or via video or telephone if required. It will be completed by a caregiver who we will refer to as a 'Study Partner'. In most cases it is anticipated this will be a parent.

Children's Sleep Habits Questionnaire - A validated measure incorporating different types of sleep disturbance and their frequency. It will also be completed by the Study Partner.

Pediatric Quality of Life Inventory – a validated measure of health-related quality of life in children including self-report and parent/carer report versions. Both will be used where possible, but this will depend on participants' age and ability to complete the self-report version.

A sleep diary to be completed by the Study Partner and which will include the following. However we recognise that some of the categories will be difficult to complete for children with very impaired cognition, self-reflection, communication and physical health/mobility

- The time the child/their carer had hoped or intended they wake up and when they actually woke up
- Whether the child woke up spontaneously or was woken e.g. by an alarm clock, carer or other disturbance
- The time the child got out of bed
- How the child felt or appeared to feel during the day (mood, drowsiness, etc.)
- Details of any daytime naps and exercises

- Caffeine consumption
- The time and type/ heaviness of evening meal
- Routine and activities in the run up to bed time
- Level of distress before bedtime
- Bedtime, sleep latency and any activities between bedtime and falling asleep
- The presumed cause, number, time, and length of any night-time awakenings and activities during these moments
- Quality of sleep
- Level of comfort of any recalled good or bad dreams

Actigraphy – participants will wear watch-like actigraphs (Somnowatch plus, Somnomedics) on a wrist or ankle continuously for a week to collect circadian rhythm data by recording levels of activity. These will be sent to participants by the study team to commence use one week preceding the date of the home visit.

2 nights of overnight simplified polysomnography – This is analysis of sleep patterns and will be conducted in participants' own homes. Researchers will visit to help to set up the equipment, but will not need to remain present overnight during data collection. Researchers will wear appropriate PPE and social distancing will be maintained wherever possible. Most if not all of the study team are fully vaccinated already. Government guidance and University of Edinburgh specific guidance regarding COVID-19 will be followed at all times. All non-invasive, reusable items will be disinfected with alcohol wipes prior to and after use. The recorded data below will take the form of a simplified version of the gold standard polysomnography used in sleep laboratories:

- Electroencephalography (EEG – measures electrical activity in the brain)
- Electrooculography (EOG – measures eye movements)
- Electrocardiography (ECG – measures electrical activity in the heart)
- Electromyography (EMG – measures electrical activity in muscle)
- Oxygen levels (SpO2)
- Video – for body position and movements
- Body movement
- Airflow (via nasal cannula)
- Pulse

Table 1 - Timeline of Study Assessments

Assessment	Screening	Recording Day 1	Recording Day 2	Recording Day 3	Recording Day 4	Recording Day 5	Recording Day 6	Recording Day 7
Assessment of Eligibility Criteria	X							
Written informed consent	X							
Demographic data, contact details	X							
Questionnaires	Provided at the time of consent to be completed sometime thereafter							
Sleep diary		X	X	X	X	X	X	X
Actigraphy		X	X	X	X	X	X	X
Overnight Simplified Polysomnography							X	X

6.2 LONG TERM FOLLOW UP ASSESSMENTS

No follow up assessments will be scheduled as part of this research study unless there is a need to repeat the polysomnography or actigraphy due to technical difficulties with the equipment.

6.3 STORAGE AND ANALYSIS OF SAMPLES

N/A

7 DATA COLLECTION

Identifiable Data

The following identifiable personal data will be collected from each participant:

- Name
- Date of birth
- Address
- Telephone number
- Email address
- Video recordings

Name, address, telephone number and email address for the person with parental responsibility providing proxy consent if the participant lacks capacity to consent for themselves will also be collected.

Linked-anonymised data

1. A standardised clinical history questionnaire – the collection of data will be maximised by follow up telephone and/or email contact.

2. A seven night sleep diary.

3. Use of watch-like actigraphs on a wrist or ankle continuously for a week to collect circadian rhythm data.

4. Two nights of simplified PSG data will be collected in participants own homes. The data will take the form of:
    - Electroencephalography (EEG – measures electrical activity in the brain)
    - Electrocardiography (ECG – measures electrical activity in the heart)
    - Electrooculography (EOG – measures eye movements)
    - Electromyography (EMG – measures electrical activity in muscle)
    - Oxygen levels (SpO2)
    - Video – for body position and movements
    - Body movement
    - Airflow (nasal cannula)
    - Pulse

All of the data will be linked-anonymised (coded) at source except for the video recordings. As it is not possible to link-anonymise or encrypt the video data, the data from the Somnomedics LAN video camera recorded using proprietary Somnomedics recording software will be transferred to University of Edinburgh by Local Area Network (LAN) cable. Information about the equipment can be found at (www. https://somnomedics.de/en/the-home-of-innovative-and-mobile-diagnostics/). The video on the camera will then be deleted prior to travelling back to Edinburgh.

7.1 Source Data Documentation

All data will be collected directly from participants or their Study Partners. Data will be either collected in person (including Polysomnography data, potentially also consent and questionnaires), following device usage (Actigraphy data), or remotely (informed consent and other documentation). Consent forms and questionnaires may also be posted back to the study team by participants. All data will be allocated a code to ensure it is linked-anonymised apart from the video recordings and the key to this code will be kept separately from the data.

8 DATA MANAGEMENT

8.1.1 Personal Data

The following identifiable personal data will be collected from each participant:

- Name
- Date of birth
- Address
- Telephone number
- Email address
- Video recordings

Name, address, telephone number and email address for the person with parental responsibility providing proxy consent if the participant lacks capacity to consent for themselves will also be collected.

Questionnaire and sleep diary data will be stored in paper form in locked cabinets in The Patrick Wild Centre, 5th Floor, Division of Psychiatry, Kennedy Tower, Royal Edinburgh Hospital, Morningside Terrace, EH10 5HF and in electronic form in password protected files in the University of Edinburgh's DataStore. It will only be accessible by researchers in the study team.

Electronic PSG data will be collected using the SOMNOtouch device and actigraphy data using the SOMNOwatch device, both manufactured by SOMNOmedics (www. https://somnomedics.de/en/the-home-of-innovative-and-mobile-diagnostics/). No personal identifiable information will be entered into the devices; the data will instead be linked-anonymised. The devices are encrypted and the data stored on them cannot be accessed without having the appropriate docking station and computer software. The data will be transferred to secure University of Edinburgh computers via the docking stations specific to the devices and hence will be stored on secure, University of Edinburgh servers. The data on the devices will then be deleted.

As the video data cannot be linked-anonymised and the camera cannot be encrypted it will transferred to a University of Edinburgh secure laptop by LAN cable after recordings are complete. The video on the camera will then be deleted prior to travelling back to Edinburgh.

Personal data collected in this study will be stored after the study finishes in electronic format on the University of Edinburgh's DataVault and in print form in locked cabinets (as described above) for 20 years. The paper records will then be shredded and electronic data deleted from DataVault.

8.1.2 Transfer of Data

We may share anonymised data with other organisations both within and without the UK who are conducting research into related conditions. Explicit consent will be sought from participants for any transfer of linked-anonymised data. Data shared are likely to be sent via email or computer networks.

Eighteen months following the completion of the study, anonymised data will be shared through the University of Edinburgh's DataShare open access data repository. It is possible that this data may be shared through other platforms in the future.

8.1.3 Data Controller

The University of Edinburgh is the data controller.

8.1.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh's Data Protection Officer (dpo@ed.ac.uk) who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

The sample size is a pragmatic number based on

1. The small number of people with SYNGAP1-related ID identified thus far in the UK
2. The primary endpoint is to develop a profile of sleep patterns in people with SYNGAP1 variants rather than to measure outcomes following an intervention

Hence a formal power calculation is not felt to be informative.

The proposed sample size is in our view realistic within a proposed recruitment period of 6 to 9 months as The Patrick Wild Centre already has close links with people across the UK who have SYNGAP1-related ID. We also have links with active support groups for people affected by the condition, which will be an advantage when recruiting participants.

9.2 PROPOSED ANALYSES

Differences between the people with SYNGAP1-related ID and controls will be assessed using conventional parametric and non-parametric statistics as appropriate for the clinical and cognitive test data. Where possible, non-normally distributed data will be transformed to allow the use of parametric statistics.

Variables from the PSG and actigraphy data that will be analysed include:

- Total non-rapid eye movement (NREM) sleep
- Total rapid eye movement (REM) sleep
- Number of transitions between NREM and REM

- Total sleep time
- Duration, type and frequency of seizure activity
- Duration and frequency of data indicative of clinical sleep disorders
- Analysis of EEG connectivity using coherence and entropy measures

The effect of age and gender will be sought by including them as covariates or fixed factors in parametric analyses or, where the data do not allow this even after transformation, through regression against the dependent variable.

Correlations will be made with information from the clinical questionnaire and sleep diary where appropriate.

10 ADVERSE EVENTS

When meeting with participants, investigators will remain vigilant for participant anxiety which may not manifest itself verbally. Recognised potential triggers of anxiety may include, but not be limited to, meeting new people and such people visiting participants' homes. Prior to visits participants will be sent a picture of research staff to try and mitigate this type of anxiety as far as possible. A range of Participant Information Sheets of varying complexity will be used to explain the study to participants as best we can and researchers will be guided by caregivers as to the best way to interact with participants and any communication aids required. We anticipate this will help to reduce anxiety too.

It is also possible that attaching the recording equipment will cause some distress to participants. As this is the first sleep study of people with SYNGAP1-related ID in their own homes, it is difficult to predict how likely this is. However, we aim to mitigate this as much as possible by sending mock-up equipment similar to the recording devices, to the participants to help them become acclimatised to it in advance of visiting to record data. Should a participant find certain pieces of equipment intolerable when we visit to complete the sleep recordings, those item(s) will be removed. If the child continues to be distressed, the entire procedure will be terminated. We will show parents how to safely remove the equipment if the child becomes distressed after we have left for the night. We will also carry a study mobile phone so that we can be contacted for advice overnight if needed. During our visits we will of course follow any advice from parents/Guardians regarding interaction with participants and will withdraw immediately if asked to do so. Although our aim is to record for 2 nights, if only 1 night's worth of data is collected, this will continue to be used in the study assuming it is of sufficient quality to be analysed.

type of study, we do not intend to report adverse events or serious adverse events to the sponsor.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the

event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be

given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

12.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

12.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

12.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place unless specific, additional consent is sought for this.

STUDY CONDUCT RESPONSIBILITIES

12.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.5 SERIOUS BREACH REQUIREMENTS

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 participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the sponsor (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the sponsor to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 20 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.7 END OF STUDY

The end of study is defined as the last participant's last day of PSG recording unless there is a need to repeat PSG or actigraphy recordings due to technical difficulties. The Investigators or the sponsor has the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and sponsor within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the sponsor via email to resgov@accord.scot. A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.8 INSURANCE AND INDEMNITY

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the sponsor responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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