Study Protocol

Clinical 2-hydroxyglutarate magnetic resonance spectroscopy in glioma

Co-Sponsors	The University of Edinburgh and/or Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
SAE	Serious Adverse Event
LGG	Lower grade glioma
2HG	2-Hydroxyglutarate
IDH	Isocitrate Dehydrogenase
WHO	World Health Organisation
UoE	University of Edinburgh

1 INTRODUCTION

1.1 BACKGROUND

Isocitrate dehydrogenase I (IDH1) mutation is an important determinant of prognosis in adult glioma, and a key molecular marker in the WHO 2016 guidelines for brain tumours. Presence of the mutation is independently associated with good outcome, and favourable MGMT status (a predictor of therapeutic response). Wild-type IDH genotype is associated with poor prognosis, even in the absence of typical aggressive imaging and histology features. IDH1 is cytosolic, whereas the IDH2 isoform is nuclear. IDH catalyses oxidation of isocitrate to alpha-ketoglutarate, citric acid cycle intermediary metabolites and oncometabolite influencing histone demethylation. IDH mutation produces a heterodimer where the mutant subunit converts alpha-ketoglutarate to 2-hydroxyglutarate (2-HG, a metabolite not present in normal or wild-type tumour cells).

2-HG can be detected non-invasively in vivo, using optimised magnetic resonance proton spectroscopy (MRS) [1]. This is the first tumour imaging biomarker which is specific to an individual genetic mutation. 2D MRS allows 2-HG to be mapped spatially. Methods for quantification of 2-HG levels have been implemented in studies of glioma [2, 3]

Although the presence of 2-HG is associated with good outcome, high or increasing levels of 2-HG appear to be associated with malignant transformation of WHO grade II glioma, and reduction in 2-HG has been demonstrated with treatment response in longitudinal studies [4].

We have previously demonstrated the feasibility of targeting biopsy based on spectroscopic tissue features, by incorporating spheroid virtual targets into neurosurgical navigation systems [5]

2-HG-optimised MRS has been applied elsewhere in glioma research, but has not previously been translated into UK cinical practice. Reliable detection of 2-HG can be technically challenging. Moreover, the exact mechanisms underlying quantitative variation in 2-HG and processes around malignant transformation have not been elucidated, and limited data exist on spatial heterogeneity of 2-HG in relation to IDH mutation within different tumoral regions.

1.2 RATIONALE FOR STUDY

The purpose of this work is to bring this advanced imaging technique to Edinburgh:

As a platform to elucidate molecular features associated with malignant transformation that affect 2-HG levels in spatially-defined regions of gliomas.

For clinical translation as part of a multi-modal imaging protocol; pre-surgical risk stratification in low grade glioma for clinical decision-making.

The proposed study is a collaboration between neurosurgery (IL, PB, JK), neuroradiology (AW, GT), physics (MT, ML, AV) and pathology (CS), within the context of the Edinburgh Brain Cancer Centre and The University of Glasgow (NF, DP, AC).

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objectives

The proposed study will:

1. Optimise MRS acquisition and metabolite estimation methodology.

2. Evaluate the feasibility and reliability of 2-HG metabolite quantification in vivo

2.1.2 Secondary Objectives

Evaluation of mutations, gene expression and associated metabolomic features associated with focally elevated 2HG and malignant transformation. To identify other genetic and chemical changes that are associated with aggressive parts of gliomas, by analysing tissue from regions that show high 2HG levels.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Assessment of 2-hydroxyglutarate measured spectroscopically in vivo in relation to IDH mutation determined from surgically resected diffuse glioma specimens.

2.2.2 Secondary Endpoint

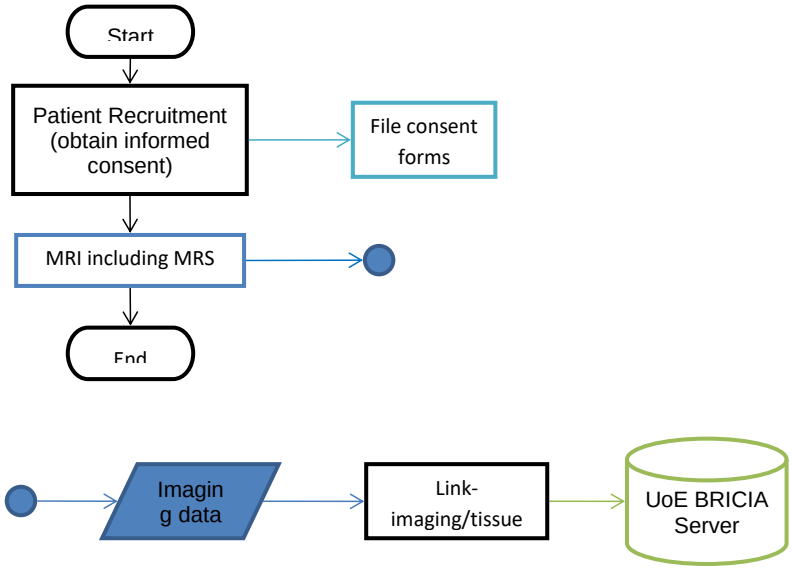
Evaluation of mutations, gene expression and associated metabolomic features associated with focally elevated 2HG and malignant transformation.

3 STUDY DESIGN

3.1 Centres

This prospective single-centre observational imaging biomarker validation study will be conducted at The University of Edinburgh (Department of Clinical Neuroscience, Royal Infirmary of Edinburgh and Edinburgh Imaging RIE facility) and The University of Glasgow (Imaging Centre of Excellence, Queen Elizabeth University Hospital)

3.2 Process flow chart



3.3 Recruitment

Patients will be recruited through the Edinburgh or University of Glasgow Neuroncology MDT or Low grade glioma clinic by one of the clinical members of the direct care team and informed consent obtained by the research nurse or one of the members of the research team.

Commented [TS1]: What is the role of the Glasgow centre?

Commented [ML2R1]: Glasgow partners will identify patients for recruitment.

Commented [TS3R1]: Will the participants then come to Edinburgh? If Glasgow is only recruiting, they could be added as a PIC (participant identification centres) – more info here. It could simplify the application and contracts process, please add more details here and select in PART C of IRAS for the Glasgow site that it is a PIC.

3.4 Schedule of assessments

Patients who have not received treatment at the time of recruitment to the study will undergo research MRI protocol within 6 weeks prior to surgery.

Patients who have previously undergone biopsy and/or surgical resection and have significant residual disease will be imaged within 6 months of tissue sampling.

3.5 Imaging schedule

MRI/MRS data will be acquired at a single timepoint, prior to surgery (or after surgical resection where there is measurable residual disease).

3.6 MRI Protocol

MRI examinations will be acquired on 3T Siemens Prisma MRI system in Edinburgh Imaging RIE facility or at the Glasgow ICE facility.

The MRI protocol will be setup by a physicist including the following sequences in addition to standard clinical sequences used in glioma assessment:

Single voxel localised MRS, optimised for detection of 2HG.

3.7 Histology

IDH-1, 1p/19q ATRX, P53 and other relevant assays will be carried out on subsequently acquired tissue samples from resection or stereotactic biopsy, as part of standard clinical care; IDH status will be compared with in vivo MRS detected 2-HG. Histological analyses will be performed by Prof Colin Smith's (NHS and University of Edinburgh) using standard clinical pathways. Additional proteomic, metabolomic and gene expression tissue analysis will also be performed.

3.8 Follow-up

Patients will have their clinical data recorded for the purpose of the study.

3.9 Data Storage and Transfer

Imaging and histology data will be anonymised and transferred to University of Edinburgh BRICIA serverencrypted so it will only be accessible by specific members of the research team. All data will be linked anonymised prior to being analysed.

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4 Study Population

4.1 NUMBER OF PARTICIPANTS

20 lower grade glioma patients (LGG) will be selected to participate in this study, recruited through the Edinburgh Neuroncology MDT or University of Glasgow Low grade glioma clinic by one of the clinical members of the direct care team.

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4.2 INCLUSION CRITERIA

- Adult subjects; 18-75 years old.
- Radiologically suspected diffuse lower grade glioma (LGG):

  1. In whom resection is planned, or

  2. Histologically-proven IDH mutant diffuse glioma and significant post-surgical tumour residuum.

  3. Must be able to provide informed consent

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4.3 EXCLUSION CRITERIA

- Any absolute contraindication to MRI.
- Patients unable to tolerate MRI, for example due to claustrophobia or inability to lie flat.
- Patients who are unable to undergo surgical tumour resection or biopsy.
- ECOG Performance status >1 (restricted in strenuous activity but ambulatory and able to carry out light work).
- Patients whose tumours are too small or in anatomical brain locations that make acquisition of satisfactory quality imaging/spectroscopy data impractical.
- Patients who are unable to give informed consent to participation.

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5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Patients will be recruited through the Edinburgh Neuroncology MDT or Low grade glioma clinic by one of the clinical members of the direct care team and informed consent obtained by the research nurse or one of the members of the research team.

5.2 CONSENTING PARTICIPANTS

Participants will have atleast 24 hours to consider the participant information sheet before being involved in the study.

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. The participant will have the option of withdrawal from:

(i) all aspects of the study but continued use of data collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Patients will be recruited for the study by members of the direct clinical care team, either at the Edinburgh site or Glasgow site. Pre-surgical patients, after being assessed for eligibility criteria and

providing consent, will undergo research MRI protocol within 6 weeks prior to surgery (at their respective site). During standard of care surgery/biopsy, a portion of the removed tissue will be used to assess molecular biomarkers for clinically relevant metabolic changes in patient's tumour.

Participants who are enrolled post-surgery with significant residual disease will undergo research MRI protocol within 6 months of their surgical resection of tissue.

Assessment	Screening	6 weeks prior to surgery	Day of surgery/biopsy	Post-surgical period (up to 6 months)
Assessment of Eligibility Criteria	☒	☐	☐	☐
Written informed consent	☒	☐	☐	☐
Demographic data, contact details	☒	☐	☐	☐
MRI/MRS scan (pre-surgical participants ONLY)	☐	☒	☐	☐
Biopsy sample collected	☐	☐	☒	☐
MRI/MRS scan (post-surgical participants ONLY)	☐	☐	☐	☒
Molecular analysis of biopsy sample	☐	☐	☐	☒

6.2 LONG TERM FOLLOW UP ASSESSMENTS

There is no plan for long term follow-up.

6.3 STORAGE AND ANALYSIS OF SAMPLES

Biopsy samples will be collected and stored within the NHS pathology lab as consistent with the standard of care.

Histologic analyses will be performed in Prof Colin Smith's laboratory using standard clinical pathways. Additional proteomic, metabolomic and gene expression tissue analysis will also be performed. Samples will be kept as with standard of care, and and histological data and analysis will be anonymised and transferred to University of Edinburgh BRICIA server. All data will be linked anonymised prior to being analysed.

The data from these biological samples will be used to correlate with the non-invasive imaging analysis to determine whether the molecular markers as determined with imaging matches with the tissue molecular markers.

7 DATA COLLECTION

Research team members will collect consent forms, patient clinical information, imaging data (MRI and MRS) and perform analysis. Data from pathological analysis will be pseudo anonymised with linking codes. The linked codes will be kept within NHS and the pseudo anonymized data will be kept with the University of Edinburgh BRICIA server. This data will all be kept within the study team and only seen by the appropriate members of the study team.

Commented [TS8]: Which one of them? The link will be in the NHSL and the pseudo-anonymise data in UoE?

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn. All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

7.1 Source Data Documentation

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

8 DATA MANAGEMENT

8.1 Personal Data

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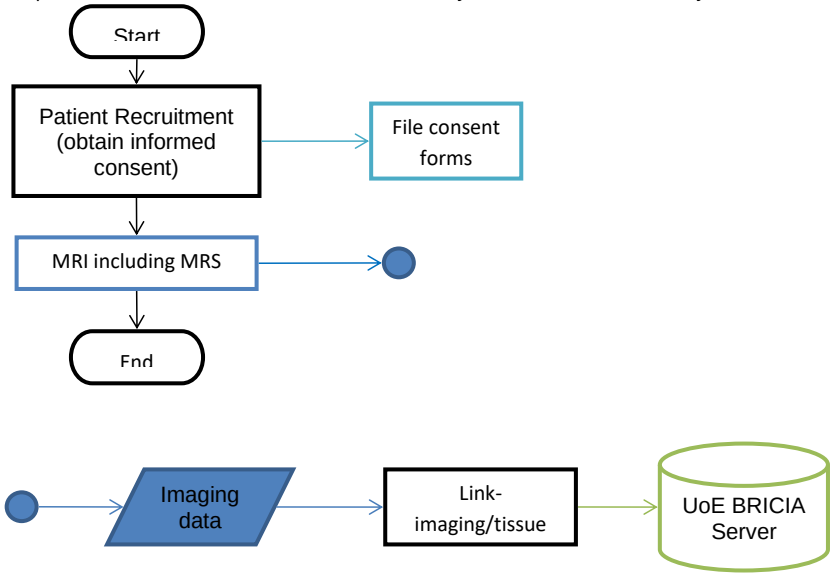
Precautions will be taken to ensure that patient confidentiality is preserved at all times. The PIS will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient. The following personal data will be collected as part of the research: CHI number which will be used to link clinical data to anonymised imaging and tissue data, medical records related to glioma treatment.

8.2 Data Information Flow

Imaging data will be stripped of patient identifiers using well-tested methods, prior to storage and analysis on University BRICIA server. Anonymized imaging/histology data from the University of Glasgow will also be stored on the BRICIA server. Imaging and tissue data will be pseudoanonymised with linking codes, which will stored securely on separate password protected media stored within the CI's pass-protected office in locked cabinets. Data will only be shared within the study team.



8.3 Data Storage

Anonymised digital data will be stored in a secure drive on the University of Edinburgh BRICIA, which is password protected and access restricted to only the specific members of the research group given permission by the University IT team.

Personal data will be physically stored by the research team at secure locked file cabinets only accessible by the CI in their pass-protected office at the Royal Infirmary of Edinburgh.

Commented [TS10]: Are the cabinets locked? Detail location.

8.4 Data Retention

Personal data and data generated by the study will be stored for 3 years.

Documents should be stored in such a way that they can be accessed/data retrieved at a later date. The data for this study will be maintained on a secure, password protected East Lothian NHS Trust computer, with only authorised personnel having access to them.

No study document will be destroyed without prior written agreement between the Sponsor and the PI. Should the PI wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

The results of the study will be written and will be submitted for publication to a suitable journal.

8.5 Disposal of Data

Anonymised imaging and tissue-derived data, and the results of comparative analyses will be stored on secure University of Edinburgh servers in the Edinburgh Imaging server.

File access is password protected and access is specifically restricted to members of the research group using specific permissions administrated by the University IT team.

Commented [TS11]: This section requests information on what happens after the retention period and disposal of data

All data will be kept for 3 years, after which it will be destroyed by University of Edinburgh-approved methods. All paper files will be kept in the locked filing cabinets in the Chief Investigator's locked office for the same period of time and destroyed fully.

8.6 External Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

8.7 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

8.8 Data Breaches

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers 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

Patient sample size was established to provide statistical significance in accordance with previous imaging biomarker studies for MRS of 2HG [6].

9.2 PROPOSED ANALYSES

Patient histology and immunohistochemistry data (IDH1/2, 1p19q, ATRX, p53 status) will be compared to quantitative MRS data and structural MRI data.

Histological analysis will be performed by pathological team. Imaging data analysis will be performed by the research team using in-house analytic scripts on MATLAB [7], and spectroscopy data will be analysed using FID-A [8] and OSPREY [9] platforms. Statistical analysis of the data will be performed using MATLAB and GraphPad Prism software [10].

10 ADVERSE EVENTS

10.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

• Results in death

• Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

• Requires hospitalisation, or prolongation of existing inpatients' hospitalisation

• Results in persistent or significant disability or incapacity

• Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

10.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

10.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

10.2.2 Serious AEs

An SAE form should be completed and sent to the Chief Investigator within 24 hours.

All SAEs should be reported to the NRES Committee London - Fulham Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form.

Local investigators should report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit study 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 a study specific risk assessment is required.

If required, a study specific risk assessment will be performed by representatives of the Sponsor(s), ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans.

If considered necessary, ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

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 necessary 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.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study 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 participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Sponsor(s).

The Investigator or delegated member of the study team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

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 study 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. 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 Data Protection Training

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance Data Protection training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

12.2.7 Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

12.2.8 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.

12.2.9 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 that could allow identification of individual participants.

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13 STUDY CONDUCT RESPONSIBILITIES

13.1 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.

Proposed amendments will be submitted to the Sponsor for classification, review and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to implementation and prior to participants being enrolled into the amended protocol.

13.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

13.2.1 Protocol Waivers

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.

13.2.2 Management of Deviations and Violations

Deviations and violations are non-compliance events discovered after the event has occurred. 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.

Deviation logs will be maintained for each site in multi-centre studies.

Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

13.3 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 study; or

(b) the scientific value of the study.

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

13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Sponsor.

13.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the Sponsor(s) have 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 R&D Office(s) and Sponsor(s) 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(s) via email to researchgovernance@ed.ac.uk.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Treatment during and following the study imaging will continue following the standard of care.

13.7 INSURANCE AND INDEMNITY

The Sponsor(s) are 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(s)' 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(s) require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 AUTHORSHIP POLICY

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

15 CONTACT DETAILS FOR REPORTING SAES

Please send SAE forms to the Chief Investigator: Prof Adam Waldman

Email: adam.waldman@ed.ac.uk Tel: 0131 465 9569

And the Sponsor – The Research and Compliance Office

E-mail: resgov@accord.scot

16 REFERENCES

References:
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