Probiotics in Paget's Disease

Study Protocol

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Funder	European Commission
Funding Reference Number	787270
Acronym	PriP study
Chief Investigator	Professor Stuart H Ralston
Sponsor number	AC20199
REC Number	*22/WS/0075*
Project registration	Not applicable
Version Number and Date	Version 6, 12/03/2024

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
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
ICH	International Conference on Harmonisation
PI	Principal Investigator
PA	Paget's Association
QA	Quality Assurance
PDB	Paget's disease of bone
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SF36	36-Item Short Form Survey
SOP	Standard Operating Procedure

INTRODUCTION

1.1 Background

Paget's disease of bone (PDB) is a common skeletal disorder characterised by increased bone turnover affecting one or more bones throughout the skeleton [1]. The most common symptom of PDB is bone pain which can be due to increased metabolic activity or complications such as bone deformity, secondary osteoarthritis, spinal stenosis, and pathological fractures. Many patients are asymptomatic however and treatment is not always required. Although genetic factors play an important role in PDB, environmental influences also contribute [2]. Many environmental triggers have been postulated to play a role including viral infections, calcium and vitamin D deficiency, mechanical loading, exposure to environmental toxins and changes in diet. More recently, the intestinal microbiome has been found to play a key role in regulating bone metabolism [3]. This has mostly been studied in preclinical models of postmenopausal bone loss [4], but clinical studies have also shown that administration of probiotics can modulate bone loss in postmenopausal women [5, 6]. Furthermore, it has also been shown that dietary induced modulation of the microbiome can modify bone and joint damage in an autoinflammatory disease caused by a missense mutation of Pstpip2 in mice [7]. Taken together this raises the possibility the dietary manipulation aimed at increasing amounts of calcium in the diet or manipulating the microbiome through changes in diet or administration of probiotics could favourably influence disease activity or symptoms of disease in patients with PDB. The aim of this study is to test this hypothesis in the context of a randomised controlled trial.

1.2 Rationale for study

Epidemiological studies have shown that environmental factors influence the occurrence and severity of Paget's disease of bone, but the identity of these factors is unclear. The present study will investigate the role of dietary calcium and vitamin D and of the microbiome as environmental factors which may modify disease activity in PDB.

There is previous evidence that dietary calcium [8] and vitamin D deficiency [9] might predispose to PDB by causing secondary hyperparathyroidism which in turn would be expected to stimulate osteoclast activity and also evidence that probiotics can favourably influence bone loss in postmenopausal women [4]. The aim of this study will be to explore the effects of dietary calcium and vitamin D supplements and probiotic supplements on biochemical markers of metabolic activity in patients with mild PDB who are not considered to require treatment with bisphosphonate therapy, and to study effects on pain and quality of life.

2. STUDY OBJECTIVES

2.1 Primary objective

To evaluate the effects of dietary calcium and vitamin D supplements, probiotics and placebo on metabolic activity of PDB as assessed by changes in serum procollagen type I N propeptide (PINP)

2.2 Secondary objective

To evaluate the effects of dietary calcium and vitamin D supplements, probiotic supplements and placebo on the following clinical and biochemical variables:

- Biochemical markers of metabolic activity in PDB other than PINP

- Health related quality of life (SF36)
- The presence and severity of pain at sites affected by PDB
- The intestinal microbiome

3. STUDY DESIGN

Randomised placebo controlled multicentre trial. An overview is provided in Figure 1.

4. INTERVENTIONS

Probiotics
The probiotic intervention will consist of three lactobacillus strains in capsular form, to be taken once daily to provide 1 x 10^{10} PFU of lactobacillus per day for 6 months. The preparation will be supplied by Probi (www.probi.com) and is identical to a supplement previously used in the prevention of postmenopausal bone loss in women [10]. The dose is one capsule per day. The capsules are made of hydroxypropylmethyl cellulose, with titanium dioxide as a colouring agent. They contain maize starch (bulking agent), magnesium stearate (processing aid) and maltodextrin (bulking agent). The capsules will be supplied by Probi (www.probi.com).

A three month supply will be dispensed at the baseline visit, the second three month supply will be given at the 3-month study visit (Table 1). Participants will be dispensed one large box (10 x 10 tablets) and one small box (1 x 10 tablets) at the first visit. They will be dispensed a large box (10 x 10) at the second visit. They will be asked to finish the first supply before they move on to the resupply.

Placebo Probiotics
The placebo probiotics consists of identical capsules containing maize starch (bulking agent), magnesium stearate (processing aid) and maltodextrin (bulking agent). A three month supply will be dispensed at the baseline visit, the second three month supply will be dispensed at the 3-month study visit (Table 1). Participants will be dispensed one large box (10 x 10 tablets) and one small box (1 x 10 tablets) at the first visit. They will be dispensed a large box (10 x 10) at the second visit. They will be asked to finish the first supply before they move on to the resupply. The dose is one capsule per day.

The probiotic and placebo capsules will be shipped by Probi under temperature-controlled conditions (2-8^{o}c) to the co-ordinating centre where it will be stored in a dedicated temperature-controlled refrigerator. The product will be shipped from the co-ordinating centre to study centres on an intermittent basis under temperature-controlled conditions (2-8^{o}c) and stored in local study centres in a temperature-controlled refrigerator. The probiotic or placebo will dispensed to participants by members of the local study team. Alternatively, and depending on local circumstances, the probiotics and placebo probiotics may instead be stored in the local hospital pharmacy and dispensed from there.

On randomisation, the local PI or delegated individual will prepare a prescription for the probiotic or placebo probiotic as appropriate. On receipt of this, a member of the local research team will dispense the appropriate number of packs to the patient.

Alternatively, if it is decided that the local pharmacy at the recruitment site will store the probiotics and placebo probiotics, these will be dispensed by the local pharmacy to the participant (or a member of the local research team) on receipt of a prescription for the probiotic or placebo probiotic.

Calcium and vitamin D

A dietary calcium and vitamin D supplement will be prescribed containing 1000 mg elemental calcium and 880 units of vitamin D in the form of AccreteD3 one a day 1000mg /880 IU chewable tablets for 6 months. Should the participant be randomised to this intervention, the calcium and vitamin D supplements will be prescribed by a member of the local study team and dispensed to participants by the local hospital pharmacy.

Table 1 summarises the number of doses of probiotics, placebo probiotics, a calcium/vitamin D supplements to be prescribed and dispensed at each visit. Copies of these prescriptions should be held in the appropriate section of the local site file.

Time-point	Probiotic dose	No. capsules	Placebo Probiotic dose	No. capsules	Calcium/Vitamin D dose	No. tablets
Baseline (0)	1 daily	120	1 daily	120	1 daily	120
3 months	1 daily	100	1 daily	100	1 daily	100

Table 1: Number of capsules to be dispensed to participants at each study visit.

Participants should be asked to return all unused study product at their final study visit. The first supply will give +/- 2 weeks window for for the 3- month visit. The resupply will allow +/- 2 weeks window for their 6-month visit.

5. ENDPOINTS

5.1 Primary endpoint

Change in metabolic activity of PDB as assessed by serum concentrations of PINP at six months

5.2 Secondary endpoints

Changes in other biochemical markers of bone metabolism including ALP, CTX, PTH and 25(OH)D

Changes in heath related quality of life as assessed by SF36

Changes in the presence and severity of pain at sites affected by PDB

Changes in the microbiome as assessed by 16S sequence analysis of stool samples

6. STUDY POPULATION

6.1 Number of participants

A total of 75 patients with PDB will be studied to give 25 patients in each treatment group

6.2 Inclusion criteria

- Clinical diagnosis of PDB confirmed by characteristic appearances on radionuclide bone scan and /or x-ray
- Serum total alkaline phosphatase elevated above the upper limit of normal or within the upper half of the local reference range, or evidence of active PDB on radionuclide bone scan within the previous two years so long as the participant has not been treated with bisphosphonates or denosumab between the scan and the baseline visit

- Willing and able to give informed consent

6.3 Exclusion criteria

- Unable or unwilling to give informed consent
- Bisphosphonate therapy thought to be indicated for treatment of PDB on clinical grounds
- Currently being treated with bisphosphonates, denosumab or calcitonin for any reason
- Currently being treated with combined calcium and vitamin D supplements
- Treatment with oral or intravenous bisphosphonates during the previous 24 months
- Treatment with denosumab during the past 12 months
- Treatment with calcitonin during the previous 3 months.
- Treatment with combined calcium and vitamin D supplements during the past 4 weeks
- Receiving probiotics during the previous 3 months.

6.4 Prohibited medications and supplements

During the trial, participants will be instructed not to take calcium and/or vitamin D supplements or probiotics other than those supplied as part of the intervention

6.5 Co-enrolment

Co-enrolment will be permitted for participants who have already been enrolled in studies that involve collection of data such as questionnaires and tissue samples such as Biobank UK and similar epidemiological studies. Co-enrolment will also be permitted for individuals who are taking part in interventional studies. This will be considered on a case-by-case basis taking into account the potential impact on both studies, subject to an agreement between both groups of investigators provided that the potential burden to participants is not considered excessive.

7. PARTICIPANT SELECTION AND ENROLMENT

7.1 Identifying participants

Potential participants will be identified by their normal health care provider through review of clinic lists at the participating study centres.

7.2 Consenting participants

Participants will be approached to take part in the study by their normal health care provider and provided with an information sheet and consent form. After being given an adequate amount of time to consider whether or not to take part (typically at least 24 hours or longer) they will be invited to provide written informed consent by a suitably qualified member of the local healthcare team or research team.

7.3 Withdrawal of participants

Subjects will be informed that they have the right to withdraw from the study at any stage without having to give a reason. They will be advised that if they do withdraw it will not impact on the normal medical care they receive. If the participant does decide to withdraw from the study, two options will be given

- Complete withdrawal: No further contact from the study team and destruction of all data gathered and all samples collected up until the point of withdrawal.
- Partial withdrawal: Termination of study procedures up to the time of withdrawal with retention of samples and data up to that point. Participant consents to being contacted by study team about future studies that may be of interest.

8. STUDY ASSESSMENTS

8.1 Baseline visit

At the baseline visit, information will be collected on past medical history, current medications and medications taken during the previous 3 months. Diet will be assessed using a validated food frequency questionnaire (the Scottish Collaborative Group FFQ). Smoking and alcohol intake will be recorded.

The sites of Paget's disease will be recorded based on review of the medical records and the results of imaging. Analysis. The presence and severity of bone pain localised to sites affected by PDB will be recorded using a visual analogue scale with ratings from 0 (no pain) to 10 (the worst pain possible). Health related quality of life including bodily pain assessed by SF36 will also be recorded

A blood sample will be taken for routine biochemistry and haematology and sent to the local laboratory for analysis. An additional blood samples will be taken for analysis of specialised markers of bone metabolism, for genetic and epigenetic analysis and for transcriptome analysis. A stool and saliva sample will be obtained for analysis of the microbiome.

Following randomisation, participants will be given 3-month's supply of the intervention (probiotic, placebo or calcium and vitamin D supplement). Participants randomised to receive the probiotic or placebo will be advised that they should store the supplement in a refrigerator during the study. Participants randomised to the calcium and vitamin D supplements will be advised that the supplements should be stored at room temperature.

8.2 Visit 1 (3 months)

This will be performed three months after commencing the supplement or placebo (with a window of 2 weeks on either side). Blood samples for biochemistry and specialised biochemistry will be repeated. Stool samples will be collected for microbiome analysis. The presence and severity of bone pain localised to sites affected by PDB will be recorded. Health related quality of life assessed by SF36 will be recorded. Any adverse events that have occurred since the baseline visit will be recorded. Capsule and tablet counts will be performed to assess adherence. Participants will be given a second 3-month supply of the intervention they have been allocated to at this visit.

8.3 End of study visit (6 months)

The end of the study visit will be performed six months after commencing the supplement or placebo (with a window of 2 weeks on either side). Blood samples for biochemistry and specialised biochemistry will be repeated. The presence and severity of bone pain localised to sites affected by PDB will be recorded. Health related quality of life assessed by SF36 will be recorded. Stool samples will be collected for microbiome analysis. Any adverse events that have occurred since the last visit will be recorded. Capsule and tablet counts will be performed to assess adherence. The schedule of study assessments is summarised in Table 1.

Table 1. Schedule of study assessments

	Baseline	3 months	6 months
Medical history	X		
Current and recent drug treatments	X	X	X
Adverse events		X	X
Blood for routine biochemistry	X	X	X
Blood for routine haematology	X		
Blood for specialised biochemistry	X	X	X
Stool sample	X	X	X
SF36	X	X	X

Pain at affected site	X	X	X
Blood for genetic analysis	X		
Blood for transcriptome analysis	X		

9. Processing and analysis of samples

All samples will be labelled with a Study ID barcode. These will be supplied to sites ahead of participant recruitment. Details of the labelling system can be found in Section 11.1.

9.1 Routine biochemistry and haematology

The samples for routine biochemistry and haematology will be analysed at the local hospital laboratories for calcium, albumin, LFT, and serum creatinine and 25(OH) vitamin D.

9.2 Specialised biochemistry

These samples will be analysed centrally. A venous blood sample of up to 10ml will be collected into a plain tube and allowed to clot. Serum will be separated on site and 1ml aliquots prepared. The separated serum samples may be stored at -20^{o}c on a short-term basis for up to 48hr before transfer to a low temperature (-70^{o}c or below) freezer for longer term storage until the sample is sent to the central laboratory. These samples will be hipped on dry ice to the co-ordinating centre at the University of Edinburgh Bone Research Laboratory or to the University of East Anglia where the biochemical analyses will be performed in collaboration with Dr Jonathan Tang and Professor William D Fraser.

9.3 Samples for Genetic and Epigenetic Analysis

Samples of up to 10ml will be collected into a potassium EDTA tube at study centres and sent in an approved container system by post to the co-ordinating centre. Alternatively, the EDTA samples may be stored at -20^{o}c on a short-term basis for up to 48hr before being frozen at -70^{o}c or below until they are shipped to the co-ordinating centre on dry ice for DNA extraction and analysis

Any unused samples will be stored for up to 15 years at the co-ordinating centre for ethically approved research projects of relevance to PDB. Consent will be sought for long-term storage of samples and explicitly for genetic analysis.

9.4 Samples for transcriptome analysis

A venous blood sample of up to 3.5ml will be collected into a PaxGene tube (or similar) for transcriptome analysis.

9.5 Samples for microbiome analysis

Stool samples will be obtained for characterisation of the intestinal microbiome. Participants will be given a container and packaging with instructions on how to collect the stool samples at home. Samples will be posted back to the study centre or sent directly to coordinating centre.

10. DATA COLLECTION AND STORAGE

Data will be entered directly onto an electronic case record form (eCRF) by research staff at the study centres. For convenience, printed copies of the CRF will be provided to study centres so that the local research teams can complete the forms prior to entering onto the CRF. Following entry to the eCRF, the data will be stored on a REDCap database held on servers at the Institute of Genetics and Cancer at the University of Edinburgh. REDCap data backups are stored locally but also a secondary copy is securely sent to an encrypted container on DataStore. Access to the database will be username and password protected and limited only to staff members integral to the study. Anonymised data will be downloaded to password protected computers for statistical analysis.

11. DATA MANAGEMENT

11.1 Personal data

No personal identifiable data that will be held on the study database. The participant's normal NHS healthcare provider will hold personal data in a recruitment log held locally for administrative purposes. **Participants will be pseudonymised using a unique study number ([PriP][Centre ID][Participant ID] i.e. PRiP001001). Linkage databases to match participants with their Study IDs for the purposes of re-contacting and accessing medical records will be held at each site and will not be accessible by the central research team.**

11.2 Transfer of Data

Data which would allow the participant to be identified (including personal data) will not be transferred to individuals or organisations outside of the NHS organisation(s) recruiting the participants.

11.3 Data controller

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 in force at the time.

11.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

12. STATISTICS AND DATA ANALYSIS

12.1 Sample size calculation

A sample size of 75 participants has been chosen to provide 25 subjects in each treatment group. The hypothesis to be tested is that we will observe a reduction of at least 0.6 of a standard deviation difference in PINP in the calcium and vitamin D group or the probiotics group as compared with the placebo group at 6 months where we expect no change to occur. According to this assumption, the sample size of 25 subjects per group will provide 82% power to detect such a change.

12.2 Proposed analyses

Analysis of the primary endpoint will be to evaluate changes in PINP in each treatment group between baseline and the study endpoint using by analysis of covariance (ANCOVA) to take account of baseline differences between groups.

Analysis of the secondary endpoints will similarly employ ANCOVA to evaluate differences between the treatment groups.

13. ADVERSE EVENTS

The Investigator, or a delegated researcher, is responsible for the detection and documentation of adverse events that may be related to participating in the study and that meet the criteria and definitions detailed below.

13.1 DEFINITIONS

An adverse event (AE) is an untoward medical occurrence in a study participant.

An adverse reaction (AR), in the context of this study, is any untoward and unintended response which is related to probiotics or dietary calcium supplements administered to that participant.

A serious adverse reaction (SAR) is any AR that:

• results in death of the clinical trial participant; is life threatening. A life-threatening AR refers to an event where the participant 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 in-patient hospitalisation^ or prolongation of existing hospitalisation;
• results in persistent or significant disability or incapacity;
• consists of a congenital anomaly or birth defect;
• results in any other significant medical event not meeting the criteria above.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by administration of the probiotics or dietary calcium supplements

^Any hospitalisation that was planned prior to randomisation will not meet seriousness criteria. Any hospitalisation that is planned post randomisation will meet the seriousness criteria unless it does not constitute an untoward medical occurrence (such as cosmetic elective surgery, social and/or convenience admission).

13.2 IDENTIFYING AEs AND ARs

All AEs and ARs will be identified from the time a participant signs the consent form to take part in the study until the completion of study follow-up.

13.3 RECORDING AEs AND ARs

All AEs, including post-operative complications, and mortality, will be recorded as part of the outcome measures in the study CRF. There is no requirement to complete an additional AE form.

13.4 Detecting adverse events

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

13.5 Assessment of causality

Should an AE or SAE occur the investigator will be asked to assess whether the event is related to the supplement and categorised as follows

Unrelated: Where the event is not considered to be related to the study supplement

Possibly Related: where the event is thought to be related to supplement based on a temporal relationship between administration of the supplement and occurrence of the event

Probably Related: Where the event is thought to be related to the supplement

13.5 Assessment of severity

Should adverse events occur that are thought to be possibly related or probably related to the supplement, the investigator will be asked to grade the severity as follows:

- Mild: an event that causes minimal discomfort and does not interfere with every day activities.
- Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: an event that prevents the participant undertaking normal everyday activities.

14. OVERSIGHT ARRANGEMENTS

14.1 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.

14.2 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.

15. GOOD CLINICAL PRACTICE

15.1 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.

15.2 Investigator responsibilities

The investigator will be 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.

15.3 Informed Consent

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

The participant will 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).

15.4 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.

15.5 Data Recording

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

15.6 Investigator Documentation

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

15.7 GCP Training

For this study, researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement. GCP training status for all investigators should be indicated in their respective CVs.

15.8 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.

15.9 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 and be of a form where individuals are not identified and re-identification is not likely to take place

16. STUDY CONDUCT RESPONSIBILITIES

16.1 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.

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.

16.2 Management of protocol non-compliance

Prospective protocol deviations, (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.

16.3 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 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 co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors 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.

16.4 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 not be destroyed without permission from the sponsor.

16.5 End of study

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

The Investigators or the co-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 co-sponsors 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 co-sponsors 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.

16. 6 Continuation of treatment following the end of study

Not applicable for this study

16.7 Insurance and indemnity

The co-sponsors 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 co-sponsors' 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 co-sponsors 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.

17. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

17.1 Authorship policy

Authorship on the publications that result from this work will be determined on the basis of ICMJE recommendations which stipulate that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The contribution of Individuals who contribute to the study but do not qualify for authorship will be acknowledged in the publication.

18. REFERENCES

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