Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease (ALL-HEART)

Data Monitoring Committee Charter

Data Monitoring Committee Roster:

DMC Members

- Professor Mark Caulfield (Professor of Clinical Pharmacology, Queen Mary University of London) [Chairperson] [redacted]
- Dr Martin Denvir, (Senior Lecturer and Honorary Consultant Cardiologist, University of Edinburgh) [redacted]
- Dr Christopher Weir (Reader in Medical Statistics, University of Edinburgh) [redacted]

DMC Contacts

- ***Sponsor:*** The UNIVERSITY OF DUNDEE and NHS TAYSIDE ("Co-sponsors")
- ***Chief Investigator:***
  Dr Isla S Mackenzie [redacted]
- ***DMC Coordinators and ALL-HEART Project Managers:***
  Mr Adam Wilson [redacted]
  Dr Suzanne Duce [redacted]
- ***Trial Statistician (blinded):*** Prof Ian Ford (Robertson Centre for Biostatistics, Glasgow) [redacted]
- ***Chair of the Trial Steering Committee (TSC):*** Prof Sir Lewis Ritchie (University of Aberdeen) [redacted]

APPROVING OFFICIALS

Name	Signature	Date
Prof Mark Caulfield DMC Chairperson	_____	_____
Dr Martin Denvir DMC Member	_____	_____
Dr Christopher Weir DMC Member	_____	_____
Dr Isla S Mackenzie Chief Investigator (Representative of the Sponsor - UNIVERSITY OF DUNDEE and NHS TAYSIDE)	_____	_____
Prof Ian Ford Trial Statistician, Robertson Centre for Biostatistics, University of Glasgow	_____	_____

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I. Scope of ALL-HEART STUDY DMC and DMC Charter

The ALL-HEART STUDY DMC (*Data Monitoring Committee*) will independently monitor patient safety and efficacy information during this study.

The objective of the ALL-HEART STUDY DMC Charter is to outline the specific purposes and functions of the DMC and the procedures for data abstraction and data delivery conventions to and from the DMC members for review purposes.

II. The role of the DMC

The DMC's main role is as follows:

- It is the only body involved in the trial that has access to the unblinded comparative data
- The role of its members is to monitor these data and make recommendations to the TSC (*Trial Steering Committee*) on whether there are any ethical or safety reasons why the trial should not continue
- The safety, rights and well-being of the trial participants are paramount
- The DMC considers the need for any interim analysis advising the TSC regarding the release of data and/or information
- The DMC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies
- If funding is required above the level originally requested, the DMC may be asked by the Chief Investigator, TSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial
- Membership of the DMC should be completely independent, small (3- 4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area or expert trial statistician
- Responsibility for calling and organising DMC meetings lies with the Chief Investigator, in association with the Chair of the DMC. The project team should provide the DMC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMC
- The DMC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be fed into the TSC
- Minutes of meetings (excluding closed sessions) should be sent to all DMC members, the sponsor, the funder, the TSC and the trial master file.

III. Standard Constitution DMC

The following list identifies the minimum constitution requirements, a set of outline terms of reference and the primary reporting line for DMC:

- Most primary research projects are required to establish a DMC
- The NIHR HTA Programme Director will vet the nominees and appoint the chair and members
- All DMC members are to be independent (with at least one member being UK based and/or holding a substantive UK based appointment)
- Only appointed members will be entitled to vote and the chair will have a casting vote
- The minimum quorum for a meeting to conduct business is 67% of appointed members
- The chair and members to sign and maintain a log of potential conflicts and/or interests
- Attendance at DMC meetings by non-members is at the discretion of the chair
- The primary DMC reporting line is via the chair of the DMC to the TSC

IV. Independence

The definition of independent is as follows:

- Not part of the same institution as any of the applicants or members of the project team
- Not part of the same institution that is acting as a recruitment or investigative centre
- Not related to any of the applicants or members of the project
- For the chair only- not an applicant on a rival proposal

V. Composition of ALL-HEART STUDY DMC

The DMC members are named on the DMC roster. The DMC will be composed of one Chairperson (Prof Mark Caulfield), one additional physician and one biostatistician with clinical trial and prior DMC experience.

The Funder, NIHR HTA, will approve and appoint all DMC members. DMC members will not be involved as investigators in the ALL-HEART study. In addition, DMC members must not have a conflict of interest that would bias their review of trial data (e.g. DMC members must not have a financial interest that could be substantially affected by the outcome of the study, strong views on the relative merits of the study drug, or relationships with individuals in trial leadership positions that could be considered reasonably likely to affect their objectivity).

All DMC members are expected to serve from study start until the study is completed (at least until end of study final database lock). Should it be necessary for a member to resign, the member must submit the effective date of resignation in writing to UNIVERSITY OF DUNDEE and NHS TAYSIDE and the DMC Chairperson. In the event a member resigns, UNIVERSITY OF DUNDEE and NHS TAYSIDE, in consultation with the DMC Chairperson and The Funder, will initiate the process to identify a replacement member.

VI. DMC Contacts and ad hoc Consultants

DMC contacts and ad hoc consultants are not considered to be members of the DMC. The official DMC contacts are named on the DMC roster.

The UNIVERSITY OF DUNDEE and NHS TAYSIDE will assign DMC Coordinators who will provide administrative, logistical, and coordinating services to the DMC.

From the Sponsor, UNIVERSITY OF DUNDEE and NHS TAYSIDE, an identified representative will serve as a primary contact person for the DMC.

The Robertson Centre for Biostatistics, University of Glasgow will assign a Biostatistician who will generate the DMC Data Reports. In addition, this individual will be available to the DMC, to provide consultation regarding the information presented within the DMC Data Reports.

The DMC may, with prior approval from UNIVERSITY OF DUNDEE and NHS TAYSIDE, contact and involve selected expert consultants who may provide additional, relevant insight or expertise to the DMC, regarding any specific issues that may arise.

As a rule, DMC contacts and consultants must not attend closed sessions of DMC Data Review Meetings. The DMC Chairperson will ensure that DMC contacts and consultants are not inappropriately exposed to fully unblinded and/or unblinded data made available to the DMC.

VII. ALL-HEART STUDY DMC Responsibilities

The ALL-HEART study DMC is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety, efficacy and other clinical trial data at regular intervals. As such, the primary objective of the DMC is to monitor the safety of the subjects in the ALL-HEART study by reviewing the available clinical data at scheduled time points at least annually, or more often as appropriate, (which may be face to face or via teleconference) and on an *ad hoc* basis as needed.

After the review of each Data Report has been completed, the DMC Chairperson will provide the official DMC recommendation to the TSC regarding the appropriateness of continuing the study, from a safety and efficacy perspective, as well as any other recommendations relevant to study conduct and/or patient safety.

The operating procedures of the DMC are based on and are in compliance with the US Food and Drug Administration's draft "Guidance for Clinical Trial Sponsors on the Establishment of Clinical Trial Data Monitoring Committees."

Specifically, the DMC members are authorised and charged to perform the following functions:

- Provide approval for and operate in accordance with the specifications outlined in this DMC Charter
- Monitor the safety of patients enrolled and to be enrolled in the ALL-HEART STUDY, and the efficacy of the trial, through scheduled review of accumulating clinical data from the ongoing clinical trial
- Review and evaluate the content of all Data Reports received
- Participate in and vote on DMC recommendations.

Throughout the trial, the DMC Chairperson will serve in a leadership role and will be authorised and charged with the following additional responsibilities:

- Conduct all DMC Data Review meetings
- Ensure that all relevant data have been reviewed by the DMC members and that all issues have been addressed
- Ensure that blinded individuals (i.e. the DMC Coordinator, DMC contacts, and DMC consultants) are not inappropriately exposed to confidential and/or unblinded data
- Ensure that only the members of the DMC are present during DMC deliberations, when DMC recommendations are discussed and DMC voting procedures are conducted
- Generate confidential, written minutes of all closed and executive sessions of any DMC Meetings and maintain these minutes as confidential to DMC members, only, until the final (end of study) database lock is complete
- Provide DMC approval of records and minutes of open and final sessions of all DMC meetings
- Maintain a secure central file of all data outputs received for DMC review and all minutes of all sessions of DMC meetings. Provide a copy of this file to UNIVERSITY OF DUNDEE and NHS TAYSIDE, once the final (end of study) database lock is complete
- Communicate, author, sign, and provide the official, final recommendations of the DMC within specified timelines and according to the specifications outlined in this charter. If the DMC is divided in opinion on any major issue affecting the DMC's recommendation to UNIVERSITY OF DUNDEE and NHS TAYSIDE, the DMC Chairperson is responsible for assembling and presenting the majority and dissenting opinions for all recommendations considered
- Arrange for consultation(s) and/or request additional data, as deemed necessary.

VIII. UNIVERSITY OF DUNDEE and NHS TAYSIDE Sponsor Responsibilities

The Co-sponsors, UNIVERSITY OF DUNDEE and NHS TAYSIDE, will have the following responsibilities with respect to the ALL-HEART STUDY DMC:

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- Ensure relevant clinical or other data available to UNIVERSITY OF DUNDEE and NHS TAYSIDE on the safety of allopurinol are provided for communication to the DMC
- Collaborate with the chief investigator to ensure that DMC members are informed of trial progress and issues on a regular basis
- In preparation for data review meetings, collaborate with the chief investigator and the Robertson Centre for Biostatistics to prepare and provide a general summary of the status of the trial and any relevant clinical issues
- Provide Sponsor representation at all open and final sessions of DMC meetings, as needed

- Arrange for fair and reasonable reimbursement to DMC members for any study-related travel costs, such as transportation, lodging, and meals for the purposes of attending DMC meetings.
- Provide a primary contact representative to receive recommendations from the DMC
- Maintain ultimate responsibility for safe study conduct.

IX. ROBERTSON CENTRE FOR BIOSTATISTICS Responsibilities

Statisticians at the Robertson Centre for Biostatistics will programme and validate the reports that will be provided to the DMC. The group at the Robertson Centre for Biostatistics that holds the randomisation codes will merge these with the study data, run the reports and make the reports available to the DMC via a secure website.

The responsibilities of the Robertson Centre for Biostatistics are as follows:

- Operate in accordance with the specifications outlined in this DMC Charter
- Work with DMC members to determine the data that are necessary for the DMC Data Reports
- Provide reports to the DMC securely and in a timely fashion.
- Maintain an archive of electronic copies of datasets, programs and reports provided to the DMC
- Provide consultation regarding the information presented in the DMC Data Reports, as requested by the DMC members.

X. DMC Coordinator Responsibilities

The UNIVERSITY OF DUNDEE and NHS TAYSIDE will provide an DMC Coordinator(s) for the ALL-HEART STUDY. The DMC Coordinator(s) will provide full administrative, logistical and coordinating support to the DMC members.

The DMC Coordinator will be charged with the following responsibilities:

- Secure approval for and operate in accordance with the specifications outlined in this DMC Charter
- Serve as the primary, central point of contact for the DMC members and as the main liaison between the ALL-HEART STUDY operations teams and the DMC members
- Coordinate the implementation of the schedule for preparation and distribution of Data Reports to DMC members
- Follow-up to verify that all data required by the DMC are provided according to an agreed timeframe
- Obtain DMC recommendation letters and distribute them, as described in this DMC Charter
- Coordinate arrangements for all data review meetings and any DMC *ad hoc* meetings, as outlined in this charter
- Maintain a central file of all key DMC-related correspondences. Provide this file to UNIVERSITY OF DUNDEE and NHS TAYSIDE after the final (end of study) database lock is completed
- UNIVERSITY OF DUNDEE and NHS TAYSIDE will process DMC member expense reports.

XI. ALL-HEART STUDY DMC Member Training

All DMC members will receive protocol overview training.

XII. Ongoing Communications & Notifications to ALL-HEART STUDY DMC

The DMC Coordinator will provide the DMC Chairperson with copies of all Safety Letters related to the ALL-HEART STUDY.

XIII. ALL-HEART STUDY DMC Data Reports

DMC members will receive all DMC Data Reports directly from the Robertson Centre for Biostatistics via a secure website.

DMC Data Reports will be provided to the DMC members at least one week prior to scheduled data review meetings.

Data included in each DMC Data Report will be cumulative-to-date at the time of the established data cut-off. The cut-off date for the data included in the Data Reports, as well as the current enrollment figures, will be stated in a cover letter.

The DMC may request additional information on individual patients, as needed.

Data Reports for review by the DMC will be presented in an unblinded fashion for both safety and efficacy reviews.

XIV. ALL-HEART STUDY DMC Meetings

DMC Data Review Meeting Frequency

Once all DMC training is complete and the DMC Charter has been finalised, the DMC data review meetings will be scheduled at least annually, or more often as appropriate.

The committee will have the opportunity to make a recommendation of early stopping because of overwhelming evidence of benefit from study treatment based on interim analyses after approximately 50% and 75% of the target number of adjudicated study outcomes have been observed. Overwhelming evidence of benefit is defined as evidence of benefit of allopurinol over usual care (P<0.001).

The DMC may formulate its own internal guidelines for monitoring other outcomes. These should be minuted.

In addition to these planned data review meetings, the DMC will have the ability to hold *ad hoc* meetings, should they be deemed necessary.

DMC Meeting Agendas

With input from the DMC Chairperson and UNIVERSITY OF DUNDEE and NHS TAYSIDE, the DMC Coordinator will establish the agenda for each planned data review meeting and for any ad hoc DMC meetings.

DMC Attendance

All three (3) DMC members must be in attendance, in order for each DMC data review meeting to be convened, and in order for voting procedures to be conducted.

DMC Meeting Structure

It is anticipated that DMC data review meetings will be either face to face or by teleconference.

DMC data review meetings will normally consist of three sessions: an open session, a closed session, and a final open session. If it is necessary for a representative of the Robertson Centre for Biostatistics to attend the closed session of an DMC meeting, then the DMC members should proceed to an executive session only including the DMC members.

During open sessions the DMC members, as well as the DMC Coordinator, the Sponsor, a representative of the Robertson Centre for Biostatistics and any other DMC contacts and consultants may be present. During open sessions, the DMC members will receive a project update and will have an opportunity to discuss the progress of the trial with a representative of the Sponsor, UNIVERSITY OF DUNDEE and NHS TAYSIDE.

Typically, only DMC members may participate in closed sessions. During closed sessions, the DMC members will confidentially review the DMC Data Report, deliberate and conduct voting procedures.

During final open sessions the DMC members, as well as the DMC Coordinator, the Sponsor, a representative of the Robertson Centre for Biostatistics and any other DMC contacts and consultants may be present. During this session, the DMC Chairperson will communicate the final recommendations directly to a representative of the Sponsor, UNIVERSITY OF DUNDEE and NHS TAYSIDE.

DMC Voting Procedures: Recommendation to Sponsor

After review and discussion of each Data Report, the DMC members will vote to determine the final DMC recommendation within one of the following four options:

- Continue the study without modification
- Continue the study and amend the protocol, as specified

- Pause enrollment, pending resolution of a specified issue
- Terminate the study.

All DMC members must participate in this voting procedure. The DMC Chairperson will document the outcome of the vote. From review of the votes, the DMC Chairperson will assess whether a consensus opinion has been achieved.

If DMC consensus is not achieved, majority vote will determine the final decision of the DMC, and the DMC Chairperson will be responsible for assembling and presenting the majority and dissenting opinions to UNIVERSITY OF DUNDEE and NHS TAYSIDE, for all recommendations considered.

If deemed necessary, the DMC may elect to postpone the determination of an DMC recommendation, pending external consultation(s) and/or receipt of additional data and a subsequent closed DMC Data Review Meeting session.

The recommendations of the DMC will be based on the members' clinical and biostatistical assessment of the cumulative safety data provided for review. As there will be interim analyses carried out, the DMC members will be guided by formal statistical stopping guidelines. As part of the recommendation to the Sponsor, the DMC may also make comments and suggestions that might enhance study performance, as deemed appropriate.

DMC Meeting Minutes

DMC Data Review meeting minutes will be divided by session and will reflect attendance, as well as whether each individual attended in person or via teleconference.

The DMC Coordinator will produce minutes of open sessions of the DMC meetings within a week of the meeting close out. The DMC Coordinator will provide draft minutes to the DMC Chairperson and UNIVERSITY OF DUNDEE and NHS TAYSIDE, for review and approval, before distribution. Once approved by the DMC Chairperson and UNIVERSITY OF DUNDEE and NHS TAYSIDE, the DMC Coordinator will distribute the final minutes as appropriate.

Since all details of DMC deliberations must be kept strictly confidential among members of the DMC, the closed and executive portions of the DMC Data Review meeting minutes must remain confidential until after the study database is locked and the treatment groups for the entire study are unblinded. The DMC Chairperson (or a designee selected among the DMC members) will produce the minutes of the closed and executive sessions of DMC meetings. These minutes will be distributed only to DMC members, for the duration of the data collection until final database lock.

The DMC Chairperson will file all minutes from all sessions, centrally. After the study database is locked and the treatment groups for the entire study are unblinded, the DMC Chairperson will forward the central file of all DMC minutes for all sessions to UNIVERSITY OF DUNDEE and NHS TAYSIDE

XV. ALL-HEART STUDY DMC Communication of Recommendation

Once the DMC recommendation is finalized by DMC vote, the DMC Chairperson will communicate the DMC recommendation to UNIVERSITY OF DUNDEE and NHS TAYSIDE, as follows:

- Initial, verbal communication of the DMC recommendation will typically occur during the final session of DMC Data Review meetings
- Formal, written communication of the DMC recommendation will take the form of an DMC recommendation letter from the DMC Chairperson and should be provided to the DMC Coordinator within one week after the DMC recommendation is finalized
- Communications of DMC recommendations will reflect the consensus opinion of the DMC members. In the event that consensus cannot be reached, majority and dissenting opinions will be summarized and presented.

The DMC Coordinator will receive the DMC Recommendation Letter and distribute it to the TSC, Sponsor, Funder and any other individuals as appropriate and as specified by UNIVERSITY OF DUNDEE and NHS TAYSIDE.

The DMC Coordinator will also provide copies of the DMC Recommendation Letters to investigators for submission to Institutional Review Boards (IRBs), upon receipt of investigator requests for this information.

XVI Implementation of ALL-HEART STUDY DMC Recommendations

Any recommendations provided to the Sponsor by the DMC will be treated as such. UNIVERSITY OF DUNDEE and NHS TAYSIDE after consultation with the study Steering Committee will hold the ultimate responsibility to implement the recommendations and take appropriate actions.

UNIVERSITY OF DUNDEE and NHS TAYSIDE will notify the DMC Chairperson in writing of actions taken in response to a given DMC recommendation, for cases in which Sponsor action other than to continue the study without modification was recommended.

XVII. ALL-HEART STUDY DMC Document Handling & Records Retention

Confidentiality

The DMC will maintain a strictly confidential relationship to the ALL-HEART STUDY data. The DMC will only reveal specific details and information associated with DMC data review to appropriate parties, as specified by this DMC Charter.

The materials provided to the DMC should be considered and handled as strictly confidential in nature, as they have the potential to contain unblinded information regarding the trial, which cannot be communicated to non-DMC members. As such, no member of the DMC should release these data – or inappropriately disclose the contents – to unauthorized persons. If a situation occurs where confidential information is released to someone outside of the DMC, the DMC Co-ordinator should be informed and he or she will follow up immediately, in consultation with the chief investigator, to establish the best course of action to maintain study integrity.

With specific reference to the above instruction, DMC members should take care to maintain the blind of the Sponsor and agents of the Sponsor (e.g., employees of UNIVERSITY OF DUNDEE and NHS TAYSIDE) at all times for the duration of the trial.

The RCB biostatisticians responsible for programming and validating the unblinded DMC materials will not discuss any unblinded information with any other individual within or out-with the team who has not been unblinded (including the trial statistician, Ian Ford).

Data Handling

The DMC Chairperson must retain a copy of all data reviewed by the DMC in a central file. The DMC Biostatistician should collect all other documentation after the meeting and dispose of it.

Records Retention

The DMC Chairperson should maintain a copy of the DMC file (i.e., copies of all data reviewed by the DMC and copies of final minutes of all sessions of any DMC meeting) until two years after the end of the ALL-HEART study. After the two-year period, the DMC Chairperson should contact the Sponsor, to determine if further retention and/or archiving are necessary.

XVIII. INDEMNIFICATION AND LIABILITY

Sponsor Indemnification

The University of Dundee (the Co-sponsor) shall indemnify, defend and hold harmless each DMC member, from and against any and all losses, damages, liabilities, reasonable attorney fees, court costs, and expenses (collectively "Losses") resulting or arising from any third-party claims, actions, proceedings, investigations or litigation relating to or arising from or in connection with the performance of responsibilities by such DMC member contemplated

herein, except to the extent any such Losses have resulted from a breach of such DMC member's obligations hereunder or from any willful or intentional misconduct of the DMC member seeking indemnity hereunder. This indemnification provision shall not extend to any claim brought against a DMC member by a Co-sponsor or their respective affiliates, its directors, officers, employees, agents and subcontractors.

DMC Member Indemnification

Each DMC member shall indemnify, defend and hold harmless each of the Co-sponsors, its affiliates, directors, officers, employees, agents and subcontractors (hereinafter collectively "Co-sponsors"), from and against any and all losses, damages, liabilities, reasonable attorney fees, court costs, and expenses (collectively "Losses") resulting or arising from any third-party claims, actions, proceedings, investigations or litigation relating to or arising from or in connection with the study ALL-HEART STUDY, provided that such Losses have resulted from any material breach of such DMC member's obligations hereunder or from a judicial finding of willful or intentional misconduct of such DMC member.

Indemnification Procedure

Each DMC member seeking indemnification from the University of Dundee hereunder shall give the University of Dundee within seven (7) days written notice of any such claim or lawsuit (including a copy thereof) served upon it and shall fully cooperate with the University of Dundee and its legal representatives in the investigation of any matter the subject of indemnification. The DMC member shall not unreasonably withhold its approval of the settlement of any claim, liability, or action covered by this indemnification provision.

A Co-sponsor seeking indemnification from any DMC member hereunder shall give such DMC member(s) prompt notice of any such claim or lawsuit (including a copy thereof) served upon it and shall fully cooperate with DMC member and its legal representatives in the investigation of any matter the subject of indemnification. The Co-sponsors shall not unreasonably withhold its approval of the settlement of any claim, liability, or action covered by this indemnification provision.

Limitation of Liability

Notwithstanding anything contained herein, neither any DMC member nor either Co-sponsor, nor any of its affiliates, directors, officers, employees, agents or subcontractors shall have any liability of any type (including, but not limited to, contract, negligence, and tort liability), for any loss of profits, opportunity or goodwill, or any type of special, incidental, indirect or consequential damage or loss in connection with or arising out of the obligations to be performed hereunder or otherwise in connection with the ALL-HEART study. In addition, the aggregate liability of the University of Dundee including for any material breach of its obligations hereunder, or otherwise in relation to the subject matter hereof (including that arising from negligence, delict, tort, or otherwise) during the ALL-HEART study or thereafter shall in no event exceed £2,000,000.

Other Remedies and Rights

The indemnification provided for herein shall be in addition, and not in limitation or in lieu of, any remedies or rights either party may have in law or equity or otherwise.