DATA MONITORING COMMITTEE CHARTER

Trial number: MeDO Trial

Trial title: Metformin as adjunctive therapy in overweight and obese patients with dengue: an open-label trial

Trial design: Open label study conducted in two phases with a dose escalation between phases

Trial sponsor: University of Oxford is the trial Sponsor and has delegated responsibility for pharmacovigilance, quality assurance and quality control, document management (including the Trial master file), database and archiving, regulatory and ethics approvals to the OUCRU CTU in Ho Chi Minh City, Vietnam. Queries relating to sponsorship of this trial should be addressed to OUCRU via the Chief Investigator.

Funder: Wellcome Trust

Number of patients: 60 obese/overweight patients between 10 and 30 years of age, admitted to Hospital for Tropical Diseases with NS1 test-confirmed dengue (10 patients for cohort 1 and 50 patients for cohort 2)

Names of site:

#	Country	City	Name of site
1	Viet Nam	Ho Chi Minh	Hospital for Tropical Disease

Chief Investigator: Dr. Sophie Yacoub
Co-Investigators: Assoc. Prof. Dong Thi Hoai Tam, Dr. Nguyen Thanh Phong, Prof. Nguyen Van Vinh Cha, Dr. Huynh Trung Trieu, Dr. Luong Thi Hue Tai, Evelyne Kestelyn, Dr. Nguyen Van Hao, Dr., Dr. Cao Thi Tam, Dr. Tran Van Diet, Dr. Nguyen Minh Nguyet, Dr. Dinh The Trung, Huynh Thi Le Duyen, Laura Rivino.

1. Data Monitoring Committee (DMC) Overview

DMC Description

This independent DMC has been convened to assess the progress of the clinical study, the safety data and provide recommendations to the sponsor. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The DMC will review cumulative study data to evaluate the primary endpoint (number of adverse events and laboratory makers of severity)), safety, study conduct, and data integrity of the study. This charter will outline the roles and responsibilities and serve as the standard operating procedure (SOP) for the DMC

1. To consider the results from interim analyses, information from the investigators and relevant information from other sources

2. In the light of 1, and ensuring that ethical considerations are of prime importance, to report (following each DMC meeting or special meeting if required) to the Trial Steering Committee (TSC) and study sponsor and to recommend on the continuation of the trial
3. To determine if additional interim analyses of trial data should be undertaken
4. To consider any requests for release of interim trial data and to recommend on the advisability of this
5. The DMC administration will be coordinated by the OUCRU-VN Clinical Trials Unit (CTU).
6. DMC activities will be independent of OUCRU staff and the trial investigators.
7. This charter will be approved by its DMC members as attested to by signature of all members.

DMC Membership

- Members will disclose conflicts of interest and will be cleared of significant conflicts of interest and potential conflicts of interest in accordance with provisions in this charter.
- DMC members will sign agreement to the confidentiality statement within this document covering DMC activities.
- Composition of membership will be:

Chairperson: Assoc. Prof. Jenny Low

Independent members: Assoc. Prof. Nguyen Thanh Hung

Dr. Phung Khanh Lam

Reporting

- Data reviewed by the DMC will be provided by the study statistician
- Recommendations identified by the DMC will be provide to the TSC, Dr, the OUCRU CTU and the MeDO study team by the DMC chairperson in accordance with this charter.
- Details of closed session deliberations (e.g., minutes) will be considered privileged and not subject to disclosure except as required by law.

2. Introduction

The purpose of this charter is to define the roles and responsibilities of the Data Monitoring Committee (DMC), delineate qualifications of the membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of the reports.

The DMC will function in accordance with the principles of the following documents: ICH GCP and the approved trial protocol and/or FDA document “Guidance for Clinical Trial Sponsors: On the Establishment and Operation of Clinical Trial Data Monitoring Committees”.

The DMC administration will be coordinated by the OUCRU-VN Clinical Trials Unit. All reports from the DMC to the TSC and investigators will be made in writing, communicated to all relevant parties and maintained with the Trial Master File, as will be the Open Statistical

Reports. Closed statistical reports and closed minutes will be maintained in a separate Statistical Master File maintained at OUCRU.

3. Study Overview/Summary

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Trial Title	Metformin as adjunctive therapy in overweight and obese patients with dengue: an open-label safety and tolerability trial
ACRONYM	MeDO (**Me**tformin in **D**engue with **O**besity)
Trial Design	Open label safety tolerability study conducted in two parts with a dose escalation. The cohort 1 (10 patients) will be provided a low dose of metformin, and the cohort 2 (50 patients) will receive a weight-based dose.
Trial Population/Participants	60 obese/overweight patients between 10 and 30 years of age, admitted to Hospital for Tropical Diseases with NS1 test-confirmed dengue.
Setting	Paediatric Ward A, Ward C and Ward D at Hospital for Tropical Diseases (HTD) in Ho Chi Minh City, Vietnam
Intervention	Metformin for 5 days vs standard of care The control group will be 60 obese/overweight dengue patients, who have been enrolled in an observational study on dengue in obesity.
Study Hypothesis	1. Metformin therapy will attenuate obesity-induced lipid-inflammatory mediators and improve clinical parameters in dengue infections. 2. Metformin will reduce viral replication through AMPK activation and immunomodulation in dengue patients with obesity.
Primary Outcome Measure	• Number of adverse events (clinical and lab parameters) between groups
Secondary Outcome Measures	• Percentage change in VCAM1, ICAM1, leptin, adinopectin, LDL, AMPK phosphorylation studies. • Fever clearance time, platelet nadir, percentage increase in hematocrit from baseline • Plasma viraemia – AUC day 3 – 6 (log10-transformed), duration from enrolment to the first undetectable viraemia, and first negative NS1 measurement • The magnitude of CD8/4+T cell and NK cell responses and T cell exhaustion markers • Differential gene expression with and without metformin
Participant follow-up	Around day 21 – 28 of illness
Study Duration	1.5 years

4. Roles and Responsibilities

This DMC will

- Meet periodically (see DMC Meetings) to review aggregate and individual subject data related to safety, efficacy, data integrity and overall conduct of the trial.
- Review interim analysis assessing safety after day 5 data is available for the first 10 patients enrolled in cohort 1.
- Review efficacy and safety of trial drug regimen (metformin) versus standard care.
- Provide recommendations to continue or terminate the trial upon these analyses.
- Communicate other recommendations or concerns as appropriate.
- Operate according to the procedures described in this charter. Follow conflict of interest guidelines as detailed below (see DMC Membership).
- Comply with confidentiality procedures as described below (see Confidentiality).
- Maintain documentation and records of all activities as described below (see DMC Meetings, DMC Reports).

DMC Chair will:

- Be responsible for the overall management of the DMC meetings and process described in this charter.
- Advise on matters of the DMC membership, conflicts of interest and other issues of DMC functioning.
- Be responsible to archive the interim analysis reports and confidential documentation of rationale for decisions made by the Board during closed sessions. These will be provided to the Principal Investigator upon completion of the trial.

Study Statistician(s) will

- Generate the analysis tables and distribute the interim report amongst the DMC members (see section “Creation of interim analysis reports” below)

Sponsor (or Designees) Roles and Responsibilities

The sponsor will directly or through delegation:

- Assure the proper conduct of the study.
- Assure collection of accurate and timely data (monitoring and data management).
- Promptly report potential safety concern(s) to the DMC.
- Communicate with regulatory authorities, IRB/EC, and investigators, in a manner that maintains integrity (e.g., blinding) of the data, as necessary. (This communication is not the responsibility of the DMC.)
- Provide funding for the study and DMC.

5. DMC Membership

As characteristic qualifications, members will:

- Work professionally and meet qualifications for their respective professions.
- Comply with accepted practices of their respective professions.
- Comply with the conflict of interest policies specified by the standard operating procedures (SOPs) of the University of Oxford to ensure that members do not have serious scientific, financial, personal, or other conflicts of interest related to the conduct, outcome, or impact of the study according to the guidelines specified below (e.g., engaged in any simultaneously occurring competitive trials in any role that could pose a conflict of interest for this study). See conflict of interest statement below.
- Be independent from the sponsor, IRB/EC, regulatory agencies, Chief investigator, or any other named Investigator, steering committee membership, advisory board membership, CEC membership, clinical care of the study subjects, or any other capacity related to trial operations.
- Not be on the list of Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) (http://www.fda.gov/foi/nidpoe/default.html) and/or debarred list of investigators (http://www.fda.gov/ora/compliance_ref/debar).
- Although each DMC member will be expected to serve for the duration of the trial, in the unlikely event that a member is unable to continue participation, the reason will be documented and a replacement will be selected by the DMC board.
- DMC members will sign a non-conflict of interest statement in regard to this study which will be on file with OUCRU-VN Clinical Trials Unit. As determined by University of Oxford, conflicts of interest and/or potential conflicts of interest (as determined by SOPs) will be reduced to the greatest extent that is consistent with assembling a highly competent DMC. Any questions or concerns that arise regarding conflicts of interest will be addressed by the DMC chairperson with input from other DMC members and sponsor as necessary.

6. DMC Meetings

Projected Schedule of Meetings

An initial meeting of the DMC will be held around the time of first subject enrollment in the study in order for the members to review the charter, to form an understanding of the protocol and definitions being used, to establish a meeting schedule, and to review the study modification and/or termination guidelines. Subsequent interim and final review meetings will be held to review and discuss interim and final study data according to an estimated schedule as described in the table. However, the DMC may choose to hold meetings more or less frequently based on their review of the data.

Timeline	***Month***	***Data Review by***	***Type of Data***
Before the study starts	19/5/2020	Entire DMC	▪ Study protocol, safety concerns, DMC Charter and associated procedures/reports. Any other requested

When day 5 data of 10 patients enrolled in the cohort 1 is available	08/2020	Entire DMC	▪ Summary tables of AEs/SAEs or event reports Any other requested data
Once every 6 months	03/2021	Entire DMC	▪ Enrolment summary ▪ Adverse events ▪ Treatment received ▪ Follow-up information ▪ Tables for overall primary and secondary endpoints, available ▪ Any other requested data
Timings of any subsequent meetings will be determined by the DMC	06/2021 – 12/2021	Entire DMC	Same as above

Meeting Format

DMC meetings will generally be conducted by teleconference and coordinated by the OUCRU-VN CTU. A quorum, defined as a minimum of 2 members (including the Chair) will be required to hold a DMC meeting. Any member of the DMC may be absent during the meeting provided data tables are circulated in advance and the member has opportunity to forward any concerns to the Chair before the meeting. Decisions of the DMC should be made by unanimous consensus. However, if this is not possible, majority vote will decide. When appropriate, DMC review may be held by email exchange in lieu of a meeting.

The statistician(s) responsible for the report preparation will attend the DMC meetings as a non-voting member in order to facilitate data presentation and follow-up reporting, unless deemed not necessary by the DMC. The meetings will include both open and closed sessions.

Open and Closed Sessions

The open session may be attended by representatives of the sponsor and study investigators. Data presented in the open session may include enrollment data, individual adverse event data, baseline characteristics, overall data accuracy and compliance data or issues, and other administrative data. Minutes of the open session will be recorded by study team members. Minutes will be finalized upon signature of the chairperson and maintained by the OUCRU CTU in accordance with applicable statutory regulation.

The closed session will be restricted to the DMC members and the trial statistician(s). Data which may compromise the integrity of the study (e.g., comparative data) will be analyzed and discussed only in the closed session. The minutes of the closed session will be recorded by the trial statistician(s). Minutes from the closed session will be recorded separately from the minutes

of the open session and stored securely by the trial statistician(s). Closed session minutes, finalized by signature of the chairperson, will be maintained in confidence and retained until discarded in accordance with applicable statutory regulation.

Following each meeting, a report separate from the minutes of the open and closed sessions will be sent to the TSC describing the DMC recommendations and rationale for such (see DMC Communication of Findings and Recommendations). This report will include a recommendation to:

- Continue the trial without modification
- Continue the trial with modification
- Stop the trial due to safety concerns
- Stop the trial for another reason

Reports will be circulated to all DMC members for their approval before being issued.

Creation & conduct of interim analysis reports

The trial statistician(s) will provide the statistical reports to the DMC. No member of the DMC will be expected to produce reports or conduct analysis. The study statistician will aid in setting-up the code for generating the interim analysis summaries in a blinded fashion, i.e. without access to the randomization assignment. The randomization list will be sent to the DMC statistician directly from the study central pharmacist.

7. Study Review Criteria/Stopping Rules and Guidelines

Guidance for the conduct of safety analyses, and guidelines/stopping rules and adaptive protocol modification will be established prior to the DMC's first evaluation of data.

Safety analyses

Rate of adverse events between groups and survival are safety endpoints. The DMC will consider grade 3 & 4 adverse events, serious adverse events, unexpected events and mortality to the Investigators as definition as below:

TABLE	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject to whom an investigational medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not

	consistent with the information about the investigational medicinal product in question set out in the Summary of Product Characteristics (SPC) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect*** ▪ Is another important medical condition****

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inparticipant admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.
***Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".
**** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs 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.
An adverse event which requires discontinuation of the study medication (Metformin):

- Severe acute renal impairment (eGFR below 30mL/min/1.73m2)
- Lactate ≥ 3 mmol/L and/or onset of metformin-related lactic acidosis.
- Severe liver involvement: AST/ALT > 400U/L (VN MoH guideline 2019 [66])
- Severe diarrhoea (≥ 5 episodes of loose stool/day)
- Hypoglycaemic episode (Blood sugar < 3.9 mmol/l OR < 70 mg/dL)
- Development of severe dengue (WHO 2009 classification)
- Intolerance of study drug (persitent vomiting, new onset rash)

Study review criteria/Stopping rules and guidelines

The DMC will perform a safety analysis after day 5 data of 10 patients enrolled into the cohort 1 is available. Stopping for harm of metformin will be considered if a safety issue emerges which is sufficiently large, in the judgement of the DMC, to suggest that continued exposure of patients to the drug is unethical. The DMC will be able to mandate additional safety analyses at any time point they deem fit.

At the interim analyses, the DMC will receive a report including summaries of enrollment, adverse events, treatment received and follow-up information, tables for overall primary and secondary endpoints available. Based on these data, the committee will make recommendations on the continuation, cessation or amendment of the study.

Adaptive Protocol Modification

There is no planned sample size re-estimation or protocol adaption; however if the DMC reveals a need, a recommendation to re-evaluate the sample size calculation or make other changes may be put forward to the Chief Investigator and Sponsor.

Consideration of External Data

The DMC will also consider data from other studies or external sources during its deliberations, if available, as these results may have a profound impact on the status of the patients and design of the current study.

8. DMC Reports

Monitoring for Efficacy and Safety

The primary charge of the DMC is to monitor the study for safety. Formal DMC reviews will occur as specified above (see Study Review Criteria/Stopping Rules and Guidelines).

Safety reporting to regulatory and ethical committees will be in accordance with the requirements of each committee and the study protocol.

Monitoring for Study Conduct

The DMC will be updated during scheduled meetings on study enrolment and major operational issues. Data to be reviewed and listed in the DMC reports includes: enrollment rates over time, time from last patient enrolled to date of report (indication of delay between follow-up and reporting), summary of protocol violations, completeness of treatment and follow-up visit data, and follow-up duration for the population included in the report, etc.

Blinding

As the dissemination of preliminary summary data could influence the further conduct of the trial and introduce bias, access to interim data and results will be confidential and strictly limited to the involved independent statistician and the monitoring board and results (except for the recommendation) will not be communicated to the outside and/or clinical investigators involved in the trial.

Preparation of Reports to the DMC

Formal DMC reviews will be based on shell table or tables and figures listing which will be circulated for review before the first meeting where trial data are reviewed. The Trial Statistician will prepare and distribute reports to the DMC. The reports will be delivered electronically and securely approximately 1-2 weeks prior to the date of each DMC meeting.

In order to provide the maximum amount of information to the DMC, the analyses will employ the most recent data (recognizing limitations thereof) available at the time of the analysis. Requests for additional data by the DMC members will be made to the DMC chair or his or her designee, who will be responsible for communicating the request with the trial statisticians.

The DMC will review the data and discuss the analyses during the closed portion of the scheduled meeting. Should the committee find it necessary to modify the study, this will be noted in the DMC minutes and the procedure outlined below will be followed.

DMC Communication of Findings and Recommendations

Following each meeting and within 2 weeks of the meeting the chair will send findings and recommendations of the DMC in writing to the TSC via the trial statistician(s). The report should include the date of the meeting, participants, data reviewed by the Committee and a recommendation to continue the trial with/without modification or to stop the trial on a specified basis. The report may include minutes of relevant non-confidential discussion points and any requests for clarification of further information.

These findings and recommendations can result from both the open and closed sessions of the DMC. If these findings include serious and potentially consequential recommendations that require immediate action, the chair will promptly notify the Chief Investigator and sponsor.

TSC's Response to DMC Findings and Recommendations

The Chief Investigator and TSC will review and respond to the DMC recommendations. The recommendations of the DMC will not be legally binding but require professional consideration by the recipients. If the DMC recommends continuation of the study without modification, no formal response will be required. However, if the recommendations request action, such as a recommendation for termination of the study or modification of the protocol, the DMC will request that the TSC provide a formal written response stating whether the recommendations will be followed and the plan for addressing the issues.

It is recognized that the TSC may need to consult with regulatory agencies or other consultants before finalizing the response to the DMC. Upon receipt, the DMC will consider the sponsor response and will attempt to resolve relevant issues, resulting in a final decision. Appropriate caution will be necessary during this process to avoid compromising study integrity or the ability of the sponsor to manage the study, should the study continue. The TSC will agree to disseminate the final decision to the appropriate regulatory agencies, IRB/EC, and investigators within an appropriate time.

In the unlikely event of irreconcilable differences, especially regarding study termination or other substantial study modifications, the DMC may decide to discontinue monitoring the current study and disband. This decision will be communicated to the Chief Investigator, TSC, and others.

Public disclosure of the sponsor's final decision or DMC recommendations will be at the discretion of the sponsor or their designee. The DMC will not make any public announcements either as a group or individually.

9. DMC Closeout

This study may be terminated under a variety of circumstances including, but not limited to, study completion, termination for overwhelming effectiveness, futility, or safety issues per protocol or DMC monitoring guidelines. A final study report will be issued to the DMC who may recommend continuing action items to the Chief Investigator and Sponsor based upon the report.

10. Confidentiality

All data provided to the DMC and all deliberations of the DMC will be privileged and confidential. The DMC will agree to use this information to accomplish the responsibilities of the DMC and will not use it for other purposes without written consent from the Sponsor. No communication of the deliberations or recommendations of the DMC, either written or oral, will occur except as required for the DMC to fulfill its responsibilities. Individual DMC members must not have direct communication regarding the study outside the DMC (including, but not limited to the investigators, IRB/EC, regulatory agencies, or sponsor) except as authorized by the DMC and the sponsor.

11. Amendments to the DMC Charter

This DMC charter can be amended as needed during the course of the study. All amendments will be documented with sequential revision dates, and will be recorded in the report from the DMC meetings. Each revision will be reviewed and agreed upon by the DMC, the Chief Investigator and the Sponsor. All versions of the charter will be archived in the Trial Master File.

12. Archiving of DMC Activities and Related Documents

All DMC documentation and records will be retained in the Trial Master File in accordance with local and international regulatory requirements.

13. Agreement of DMC Members and Sponsor

Agreement of DMC Members

Agreement of the contents of this charter should be obtained by all DMC members and documented in the minutes of the initial meeting.

Name:	Date:	Signature:
Name:	Date:	Signature:
Name:	Date:	Signature:
Name:	Date:	Signature:

Agreement of Sponsor

Signatures below confirm the agreement of the Sponsor with the contents of this charter

Name:	Date:	Signature: