Charter & Working Practice Document

Independent Data Monitoring Committee (IDMC)

Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS)

Trial Identifiers

ISRCTN 47823388
EudraCT number: 2007-006749-42
MHRA reference: 03057/0027/001-0001
MREC reference: 08/H1102/112
Sponsor: University of Nottingham
Sponsor's reference: 31350

IDMC roster:

Chair of Trial Steering Committee (TSC):	Dr Helen Rodgers (Newcastle, UK)
Chief Investigator:	Professor Philip Bath (Nottingham, UK)
Trial Manager:	Mrs Sally Utton (Nottingham, UK)

IDMC Members:

a. Professor Ian Ford (Glasgow, UK) – Professor of Medical Statistics, and Chairman of TARDIS IDMC
b. Dr Cathie Sudlow (Edinburgh, UK) – Consultant Neurologist and Senior Lecturer
c. Dr Matthew Walters (Glasgow, UK) – Consultant Stroke Physician and Reader in Medicine
d. Dr Didier Leys (Lille, France)

Unblinded Statistician:
Clinical Trials Unit (University of Nottingham, UK)

I Scope of TARDIS IDMC Charter

The TARDIS Independent Data Monitoring Committee (IDMC) will independently monitor patient safety and efficacy information, and study conduct, during the period of the trial.

The objective of the TARDIS IDMC Charter is to outline the specific purposes and functions of the IDMC and those supporting its activities, and the procedures for data abstraction and data delivery to and from the IDMC members for review purposes.

II Composition of the TARDIS IDMC

The IDMC will comprise three (4) members: one Chairman, and three (3) individual members, including one international member. The IDMC members will include two physicians with stroke expertise as well as a Biostatistician with clinical trial and prior IDMC experience. Prof. Ian Ford will serve as Chairman of the IDMC. Additional IDMC members are named on the IDMC roster. The Sponsor, University of Nottingham, will approve all IDMC members.

IDMC members will not be involved as investigators in the TARDIS study. In addition, IDMC members must not have a conflict of interest that would bias their review of trial data (e.g. IDMC 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, relationships with individuals in trial leadership positions that could be considered reasonably likely to affect their objectivity, or involvement in any potential competing trial).

All IDMC members are expected to serve from study start until the study is completed, as defined by final database lock. Should it be necessary for a member to resign, the member must submit the effective date of resignation in writing to the Sponsor, IDMC Chairman, and Chief Investigator. In the event a member resigns, the Sponsor, IDMC Chairman and Chief Investigator, will initiate the process to identify a replacement member.

III IDMC Contacts and *ad hoc* Consultants

IDMC contacts and *ad hoc* consultants are not considered to be members of the IDMC. The official IDMC contacts are named on the IDMC roster and will be appointed as follows:

The University of Nottingham will assign an IDMC Coordinator who will provide administrative, logistical, and coordinating services to the IDMC. The IDMC Coordinator will serve as the primary, administrative point of contact for communications with the IDMC members and IDMC-related issues and will interface with the Sponsor and the operational leads on the project team, as appropriate.

The Sponsor will assign an unblinded statistician who will generate data and reports for the IDMC to review. In addition, this individual will be available to the IDMC, to provide consultation regarding the information presented within the IDMC reports.

The Chair of the Trial Steering Committee will serve as a primary contact person for the IDMC and IDMC issues (refer to Appendix A for communication flow). The Chief Investigator will be copied into correspondence.

The IDMC may, with prior approval from the Sponsor, contact and involve selected expert consultants who may provide additional, relevant insight or expertise to the IDMC, regarding any specific issues that may arise.

As a rule, IDMC contacts and consultants must not attend closed sessions of IDMC Data Review Meetings with the exception that the IDMC may elect to involve the unblinded Biostatistician in closed session meetings.

The IDMC Chairman will ensure that IDMC contacts and consultants are not inappropriately exposed to unblinded data made available to the IDMC.

IV TARDIS IDMC responsibilities

The TARDIS IDMC 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 IDMC is to monitor the safety of the subjects in the TARDIS study by reviewing the available clinical data at scheduled time points including twice yearly meetings (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 IDMC Chairman will provide the official IDMC recommendation to the Sponsor via the chief investigator and to the chair of the trial Steering Committee 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.

Specifically, the IDMC members are authorised and expected to perform the following functions:

- Safeguard the interests of trial participants.
- Provide approval for and operate in accordance with the specifications outlined in this IDMC Charter.
- Monitor the safety and efficacy of the trial intervention, through scheduled review of accumulating clinical data from the ongoing clinical trial and taking into account information from external sources.
- Consider the need for additional unscheduled reviews of study data.
- Review and evaluate the content of all unblinded Data Reports received.
- Ensure the confidentiality of all information received relating to the trial.
- In the event of further funding being required, to provide to the TSC and funder(s) appropriate information and advice on the data gathered to date in a manner that will as far as possible protect the integrity of the study.

- Participate in and vote on IDMC recommendations bearing in mind the fact that ethical considerations are of prime importance.

- Make clear recommendations to the Sponsor and to the Trial Steering Committee.

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

- Chair all IDMC Data Review meetings.

- Ensure that all relevant data have been reviewed by the IDMC members and that all issues have been addressed.

- Ensure that blinded individuals (i.e. the IDMC Coordinator, IDMC contacts, and IDMC consultants) are not inappropriately exposed to confidential and/or unblinded data.

- Ensure that only the members of the IDMC are present during IDMC deliberations, when IDMC recommendations are discussed and IDMC voting procedures are conducted.

- Generate confidential, written minutes of all closed sessions of any IDMC Meetings and maintain these minutes as confidential to IDMC members, only, until the final (end of study) database lock is complete.

- Provide IDMC approval of minutes of open and final sessions of all IDMC meetings.

- Maintain a secure central file of all data outputs received for IDMC review and all minutes of all sessions of IDMC meetings. Provide a copy of this file to the Sponsor, through the Chief Investigator, once the final (end of study) database lock is complete.

- Communicate, author, sign, and provide the official, final recommendations of the IDMC within specified timelines and according to the specifications outlined in this charter. If the IDMC is divided in opinion on any major issue affecting the IDMC's recommendation to the Sponsor and Trial Steering Committee, the IDMC Chairman 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.

V Sponsor responsibilities

The Chief Investigator, on behalf of the Sponsor, will have the following responsibilities with respect to the TARDIS IDMC:

- Provide final approval of the IDMC Chairman and Members to serve on the IDMC.

- Ensure relevant clinical or other data on the safety of study interventions are provided to the IDMC.

- Ensure that IDMC members are informed of trial progress and issues every 6 months.

- In preparation for data review meetings, ensure that the IDMC receive a general summary of the status of the trial and any relevant clinical issues.

- Provide representation at all open and final sessions of IDMC meetings, as needed.

- Provide final approval, in conjunction with the IDMC Chairman, of minutes of open and final sessions of IDMC meetings, as required.

- Arrange for fair and reasonable reimbursement to IDMC members for their data monitoring activities (any study-related travel costs, such as transportation, lodging, and meals).

- Provide a primary contact representative to receive recommendations from the IDMC.

- Maintain ultimate responsibility for safe study conduct.

VI Unblinded Statistician responsibilities

The Chief Investigator, on behalf of the Sponsor, will provide an unblinded statistician in support of the IDMC process. The responsibilities of the unblinded statistician are as follows:

- Provide approval for and operate in accordance with the specifications outlined in this IDMC Charter.

- Work with IDMC members to determine the data that are necessary for the IDMC Data Reports.

- Create computer programmes to generate the IDMC Data Report and transfer those reports to IDMC members in a secure and confidential manner.

- Ensure that the content of unblinded study reports or details of discussions at IDMC meetings are treated in the strictest confidence and are not revealed to any non-IDMC member prior to study closedown, without the written approval of the IDMC Chairman.

- Maintain a secure and confidential archive of electronic copies of datasets and related programs provided to the IDMC Biostatistician.

- Provide consultation regarding the information presented in the IDMC Data Reports, as requested by the IDMC members.

VII IDMC Coordinator responsibilities

The Chief Investigator, on behalf of the Sponsor, will provide an IDMC Coordinator. The IDMC Coordinator will provide administrative, logistical and coordinating support to the IDMC members. The IDMC Coordinator will be charged with the following responsibilities:

- Provide approval for and operate in accordance with the specifications outlined in this IDMC Charter.
- Serve as the primary, administrative point of contact for the IDMC members and as the main liaison between the TARDIS operations teams and the IDMC members.
- Coordinate the implementation of the schedule for preparation and distribution of Data Reports to IDMC members.
- Follow-up to verify that all data required by the IDMC is provided according to an agreed timeframe.
- Coordinate arrangements for all data review meetings and IDMC ad hoc meetings, as outlined in this charter.
- Maintain a central file of all key IDMC-related correspondences.
- Receive and arrange payment of IDMC member invoices and expense reports, e.g. for travel to/from IDMC meetings (as necessary and according to University of Nottingham reimbursement regulations).

VIII IDMC Member involvement in protocol review and training

All IDMC members will have the opportunity to review and comment on the study protocol and any proposed amendments to the protocol. The IDMC Chairman will attend an investigator training meeting prior to the study start. The Chief Investigator will respond to all queries from the IDMC on details of the protocol or proposed amendments.

IX IDMC Data Reports

IDMC members will receive all IDMC Data Reports directly from the unblinded statistician.

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

Data included in each IDMC 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 enrolment figures, will be stated in the report.

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

Data Reports for review by the IDMC will be presented on a Group A, Group B basis. The IDMC members will be informed separately of the true treatment assignments associated with the groups.

During the period of recruitment into the study, the unblinded statistician will perform interim analyses on major outcome events (including efficacy, safety and serious adverse events) along with any other analyses that the committee may request.

In the context of TARDIS, the balance between safety and efficacy should be considered.

With respect to safety the following outcomes in particular will initiate discussion and minuting of detailed reasons for recommending early stopping or continuation of the study:

- The primary outcome ('shift' in modified Rankin Scale in patients having a recurrent stroke event or TIA) favours the control group (who receive standard antiplatelet therapy but not clopidogrel), P<0.01 (nominal, 2-sided).
- Combined outcome of fatal or non-fatal stroke or major bleeding ‡ favours the control group, P< 0.01 (nominal, 2-sided).
- The overall rate of symptomatic intracranial haemorrhage exceeds 2%.[4]
- During the start-up phase, major bleeding favours the control group, P< 0.01 (nominal, 2-sided).

In making any decision, the committee will consider the overall internal and external evidence, the multiplicity of testing and the possibility that the trends in the data might be reversed with longer follow-up or increased recruitment.

With respect to efficacy, the committee will conduct formal interim analyses, after 40% and 70% of the target number of participants have been enrolled and had their 90 day outcome assessed, based on the following outcome.

- Combined outcome of fatal or non-fatal stroke or major bleeding ‡ event favours the clopidogrel group, P < 0.001 (2-sided)

In making any decision, the committee will consider the overall internal and external evidence.

‡ Bleeding is defined as:

- Major:[5] All major bleeds will constitute a serious adverse event.
  - Fatal bleeding, and/or
  - Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
  - Bleeding causing fall in haemoglobin of 2 g/l (1.24 mmol/l) or more, or leading to transfusion of 2 or more units of whole blood or red cells.
- Moderate: Moderate bleeds may or may not constitute a serious adverse event depending on other criteria as determined by the investigator.
  - Not major, and
  - Bleeding causing fall in haemoglobin of less than 2 g/l (1.24 mmol/l), and leading to no transfusion, or transfusion of only 1 unit of whole blood or red cells.
- Mild: Mild bleeds cannot constitute a serious adverse event.
  - Not major or moderate, and
  - Comprising bruising, ecchymoses, gingival bleed or similar other type bleeding.

In the light of these analyses, the IDMC will advise the Chairman of the Trial Steering Committee (TSC) and Sponsor (via the Chief Investigator) if, in their view, the randomised comparisons in TARDIS have provided both (i) "proof beyond reasonable doubt" that for all, or for some, specific types of patient, treatment is clearly indicated or clearly contraindicated, and (ii) evidence that might reasonably be expected to influence materially the patient management of the many clinicians who are already aware of the results of any other relevant trials.[1,2]

On the basis of information supplied by the IDMC, the TSC can then decide whether to modify intake to the study (or to seek extra data). Unless this happens, however, the TSC, the collaborators, and the central administrative staff (except the unblinded statistician) will remain ignorant of the interim results.

X IDMC Committee meetings

The committee will convene mainly via telephone conferences which should take place as soon as reasonably possible after the committee members have received data from the trial statistician; discussions must include all three members. Meetings should take place at least 6 monthly, or more frequently if necessary. The meeting will be organised by the IDMC coordinator and will commence with an 'open' session which will also be attended by the Chief Investigator (or representative) who will give an update on the trial's status. This will be followed by the 'closed' session attended by IDMC members only. 'Open' session minutes will be taken by the IDMC coordinator and circulated for approval and 'Closed' minutes and recommendation will be drafted by the IDMC Chairman and agreed by the IDMC members. The IDMC Chairman will report to the Chairman of the TSC with a copy to the Chief Investigator.

XI IDMC Data

Data tables, listings and graphical displays will be reported as appropriate for the whole trial, and for clopidogrel versus no clopidogrel based on the following data. The IDMC will receive a mock-up of the Report for approval prior to the first meeting at which data will be reviewed. Data will be listed by Groups A and B (in case the report becomes 'lost') where A stands for Active (i.e. Clopidogrel).

Trial status:

- Timeline for trial.
- Number of patients randomized.
- Cumulative recruitment graph.
- Discontinuation data including reasons for discontinuation.
- Completeness of data from investigators for baseline, day 7, and day 35 forms.
- Completeness of data from outcome assessor(s) for day 90 form.
- Number randomised in each centre by country.

Baseline (pre-randomisation) data:

- Demographic: Age; sex; race/ethnicity; time for stroke/TIA to randomisation; time from admission to randomization.
- Stroke: Type (infarct/no lesion seen, haemorrhagic transformation, non-stroke lesion); subtype (Oxfordshire Community Stroke Classification); aetiology (modified TOAST); severity (NIHSS).

- TIA: ABCD2 score; crescendo; already on dual therapy.
- Clinical: Blood pressure (systolic, diastolic), heart rate.
- Treatment: prior antiplatelets (aspirin, dipyridamole), antihypertensive and lipid lowering medications.

Day 7 (+/- 1 day) data:

- Number of patients with data.
- Secondary outcomes: Recurrent stroke (any infarct, haemorrhage, type not known; fatal, non-fatal); myocardial infarction (NSTEMI, STEMI); unstable angina; peripheral arterial event; deep vein thrombosis; pulmonary embolus.
- Safety: Death; neurological deterioration (NIHSS day 7 – NIHSS baseline); symptomatic intracerebral haemorrhage (SICH); major extracranial bleeding; major bleeding; moderate bleeding; minor bleeding; serious adverse events.
- Treatment: antiplatelets (aspirin, dipyridamole, clopidogrel, so deriving treatment cessation); antihypertensive medications; lipid lowering medications; carotid endarterectomy.

Day 35 (+/- 3 days) data:

- Number of patients with data.
- Secondary outcomes: Recurrent stroke (any infarct, haemorrhage, type not known; fatal, non-fatal); MI; ACS; PAD; DVT; PE.
- Safety: Death, neurological deterioration (NIHSS day 7 – NIHSS baseline); symptomatic intracranial haemorrhage (SICH); major extracranial bleeding; major bleeding; moderate bleeding; minor bleeding; serious adverse events.
- Treatment: antiplatelets (aspirin, dipyridamole, clopidogrel, so deriving treatment cessation); compliance with clopidogrel (% of blister pack taken); antihypertensive medications; lipid lowering medications; carotid endarterectomy.

Day 90 (+/- 7 days, end of follow-up):

- Primary outcome: ordinal recurrent stroke based on modified Rankin Scale (mRS) - fatal stroke (mRS=6) / mRS=5 / mRS=4 / mRS=3 / mRS=2 / mRS=1 / mRS=0 / TIA, no stroke or TIA.
- Secondary outcomes: Binary recurrent stroke; ordinal vascular event – fatal / non-fatal / no event; binary vascular event; ordinal dependency (mRS 6/5/4/3/2/1/0); death/dependency (mRS 2-6/0,1); Barthel Index (<60/60-100).
- Safety: ordinal bleeding – fatal bleed / major bleed / moderate bleed / mild bleed / no bleed; major bleeding.
- Serious adverse events: number; number during follow-up; type; fatal; SUSARs.

Pre-specified subgroups:

- Recurrent stroke by baseline groups:
    - Stratification variables: Country; ischaemic stroke/TIA
    - Minimisation variables: Age; sex; systolic BP; time to randomisation; NIHSS; ABCD2 score; crescendo TIA; event on dual/mono antiplatelets therapy; use of gastro-protection; baseline Hb

XII Records Retention

The IDMC Chairman will return a copy of the IDMC file (i.e., copies of all reports reviewed by the IDMC and copies of final minutes of all sessions of any IDMC

meeting) to the Chief Investigator after the end of the study. It will be the responsibility of the Chief Investigator, on behalf of the Sponsor, to arrange for long-term archiving.

XIII Indemnification and Liability

The Sponsor shall indemnify, defend and hold harmless each IDMC 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 IDMC member contemplated herein, except to the extent any such Losses have resulted from a breach of such IDMC member's obligations hereunder or from any wilful or intentional misconduct of the IDMC member seeking indemnity hereunder.

Version control

5 November 2010: V1.0
6 December 2011: V1.1
28 February 2013: v1.2, Staff changes, addition of new member

References

1. DAMOCLES study group. A proposed charger for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005;**365:**711-22.
2. Grant AM, Altman D, G,, Babiker AB, et al. Issues in data monitoring and interim analysis of trials. *Health Technology Assessment* 2005;**9**(7)**:**1-237.
3. Bath PMW, Gray LJ, Wahlgren NG. Should data monitoring committees assess the efficacy when considering safety in trials in acute stroke? *International Journal of Clinical Practice* 2007;**61**(10)**:**1749-55.
4. Kennedy J, Hill MD, Ryckborst K, et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurology* 2007;**6:**961-969.
5. Schulman S, Kearon C, on behalf of the subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis* 2005;**3:**592-694.

Appendix 1: Contact details

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