Fluoxetine Or Control Under Supervision (FOCUS)

A multicentre randomised trial to establish the effect(s) of routine administration of Fluoxetine in patients with a recent stroke
FOCUS

Independent Data Monitoring Committee (IDMC)

Charter & Working Practice Document

Trial Identifiers

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Funders	Stroke Association 01/04/2012 to 31/03/2015 NIHR HTA 01/10/2014 to 31/03/2019
Funding Reference Numbers	TSA 2011101 NIHR HTA 13/04/30
Chief Investigators	Professor Gillian Mead & Professor Martin Dennis
EudraCT Number	2011-005616-29
CTA Number	01384/0221/001-0001
REC Number	11/SS/0100
ISRCTN Number	ISRCTN83290762

History	Version and Date	Reason for update
	Version 2 (Draft) 17/07/12	
Updated	Version 2 30/09/15	1. New funder added. 2. Addition of competing interests forms

IDMC Members

IDMC Co-ordinator & Unblinded Statistician	Catriona Graham (Edinburgh, UK)	C.Graham@ed.ac.uk
IDMC Chair	Professor Peter Langhorne (Glasgow, UK)	Peter.Langhorne@glasgow.ac.uk
IDMC Members	Professor Helen Rodgers (Newcastle, UK)	helen.rodgers@ncl.ac.uk
	Ms Fiona Reid (Kings College London, UK)	fiona.reid@kcl.ac.uk
Chief Investigator(s)	Professor Gillian Mead	Gillian.E.Mead@ed.ac.uk
Chief Investigator(s)	Professor Martin Dennis	Martin.dennis@ed.ac.uk

Approval signatures

The following individuals, by providing their signatures, indicate their understanding of and willingness to comply with the roles and responsibilities assigned to them in this Charter.

IDMC Member	Role	Signature	Date
Professor Peter Langhorne (Professor of Stroke Care)	IDMC Chair		
Professor Helen Rodgers (Clinical Professor of Stroke Care)	IDMC member		
Ms Fiona Reid (Statistics and Trial Methodology)	IDMC member		17/3/16
Ms Catriona Graham	Unblinded Statistician & IDMC Co-ordinator		
Professor Gillian Mead	Co- Chief Investigator		
Prof Martin Dennis	Co- Chief Investigator		

I Scope of FOCUS IDMC Charter

The FOCUS 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 FOCUS 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 FOCUS IDMC

The IDMC will comprise three (3) members. The IDMC members will include two physicians with stroke expertise as well as a Biostatistician with clinical trial and prior IDMC experience. The Sponsor, University of Edinburgh, will approve all IDMC members.

IDMC members will not be involved as principal investigators or subinvestigators in the FOCUS 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 Edinburgh 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 liaise 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 Chief Investigators will serve as a primary contact person for the IDMC and IDMC issues (refer to Appendix A for communication flow).

The IDMC may, with prior approval from the Sponsor, contact and involve selected expert consultants who may, in strict confidence, 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 FOCUS IDMC responsibilities

The FOCUS 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 FOCUS study by reviewing the available clinical data at scheduled time points including at least 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 investigators 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.

The IDMC will not be asked to make any recommendations of whether the trial should be stopped on the basis of futility i.e. that the trial if it recruits to its targets sample size is unlikely to demonstrate a benefit from the trial Fluoxetine.

Throughout the trial, the IDMC Chairman will take responsibility for the Committee's operation and will be authorised and charged with the following 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.

- Ensure the generation of 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.

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

- 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.

- If deemed appropriate by the IDMC, at appropriate intervals, arrange a teleconference meeting with the Chairs of the IDMC committees for the AFFINITY and EFFECTS trials (and any other ongoing RCT of Fluoxetine in stroke which has been developed in Association with the FOCUS trial investigators). If necessary, to discuss accumulating data in strict confidence and any implications for the continuation of each of the trials. Each Chairperson may then need subsequently to consider whether to arrange a meeting of their respective trial IDMC to discuss any issues which arise from this liaison group.

V Sponsor responsibilities

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

- Provide final approval of the IDMC Chairman and Members to serve on the IDMC.
- Ensure relevant external 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 12 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.
- Attend all open and final sessions of IDMC meetings, as needed.
- 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 Investigators, 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 prior approval.
- 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 Investigators, 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 FOCUS 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 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 Investigators, once the final (end of study) database lock is complete.

- 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 Edinburgh 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 Chief Investigators 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 FOCUS, the balance between safety and efficacy should be considered.

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

- Dependency: modified Rankin Scale (mRS);

Serious adverse events (SAEs), in particular

- all-cause mortality
- stroke/TIA
- myocardial infarction
- upper gastrointestinal bleeding
- serious falls
- serious fractures
- epilepsy/seizures
- attempted suicide/self-harm
- hyponatraemia
- neuroleptic malignant syndrome-like events
- anaphylactoid reactions
- serotonin Syndrome
- pancytopenia, thrombocytopenia or haemolytic anaemia

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.

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 FOCUS 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.(DAMOCLES study group 2005; Grant, Altman et al. 2005) .Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but the DMC will work on the principle that a difference of at least 3 standard errors in an interim analysis of a major outcome event (e.g. death from all causes or independent survival at six months) may be needed to justify halting, or modifying, a study before the planned completed recruitment. This criterion has the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed.

Following a report from the DMC, the steering committee will decide whether to modify entry to the study (or seek extra data). Unless this happens however, the steering

committee, the collaborators and central administrative staff 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 12 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(s) (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 Chief Investigator(s).

XI IDMC Data

Data tables, listings and graphical displays will be reported as appropriate for the whole trial, and for Fluoxetine group and Placebo group 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 the labels Fluoxetine and Placebo however this report must be encryptyed/password protected with passwords communicated securly and changed for every report.

Trial status:

- Timeline for trial.
- Number of patients randomized.
- Cumulative recruitment graph.
- Discontinuation data including reasons for discontinuation.
- Completeness of data for baseline (day 0), discharge, 6 months and 12 months..

Baseline (pre-randomisation) data:

- Demographic: Age; sex; ethnic group.
- Stroke management:
    - Inpatient vs outpatient at time of randomization
    - time from stroke to randomization;
-
- Predicted outcomes based on Counsel model
- Motor deficits
- Aphasia
- Depression (based on PDQ 2)

Discharge (for inpatients) data:

- Number of patients with data.
- Safety: Serious adverse events (SAEs)
- Adherence with trial medication

6 months data:

- Number of patients with data.
- Safety: Serious adverse events (SAEs)
- Adherence with trial medication
- *Primary outcome* modified Rankin Scale (mRS);

12 *months data:*

- Number of patients with data.
- Safety: Serious adverse events (SAEs)
- Adherence with trial medication

Primary outcome modified Rankin Scale (mRS);

XII Records Retention

The IDMC Chairman will ensure 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) is sent to the Chief Investigator(s) 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 (and their employer where their IDMC member duties are undertaken in the course of their employment), 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.

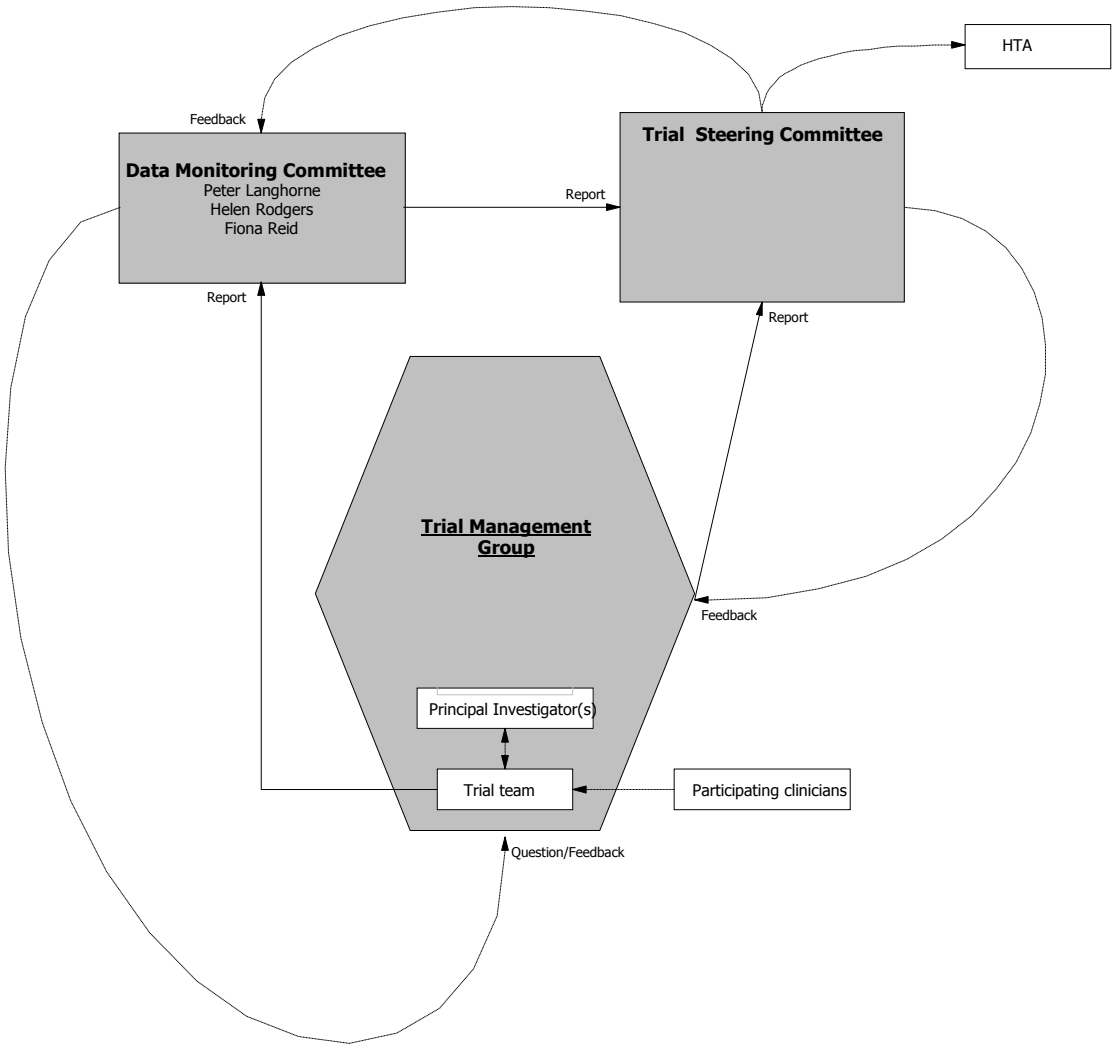
References

DAMOCLES study group (2005). "A proposed charger for clinical trial data monitoring committees: helping them to do their job well." Lancet **365**: 711-722.

Grant, A. M., D. Altman, G,, et al. (2005). "Issues in data monitoring and interim analysis of trials." Health Technology Assessment **9**(7): 1-237.

APPENDIX A

COMMITTEE COMMUNICATION FLOW



Annexe 1

Agreement and competing interests form for members of the FOCUS Trial Independent Data Monitoring Committee

Please complete the following document and return by post or scan and email to: Karen Innes, Trials Manager, Centre for Clinical Brain Sciences (CCBS), University of

Edinburgh, Chancellor's Building, Room FU303C, 49 Little France Crescent, Edinburgh, EH16 4SB, Tel: 0131 465 9610 karen.innes@ed.ac.uk

☐ I have read and understood the IDMC charter Version 2.0 dated 30/09/2015

☐ I agree to continue to be a member of IDMC for this trial as an independent member

☐ I agree to treat all sensitive trial data and discussions confidential

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC. Table 1 lists potential competing interests.

Table 1: Potential competing interests for independent members

1. Stock ownership in any commercial companies involved.
2. Stock transaction in any commercial company involved (if previously holding stock)
3. Consulting arrangements with the Sponsor
4. Frequent speaking engagements on behalf of the intervention
5. Career tied up in a product or technique assessed by the trial
6. Hand-on participation in the trial
7. Involvement in the running of the trial
8. Emotional involvement in the trial
9. Intellectual conflict e.g. strong prior belief in the trial's experimental arm
10. Involvement in regulatory issues relevant to the trial procedures
11. Investment (financial or intellectual) in competing products
12. Involvement in the publication

☒ **NO,** I have no competing interests to declare

☐ **YES,** I have competing interests to declare (please detail below)

_____

_____

Name: ___FIONA REID_____

Signed: ____ Fiona Reid. _____ Date: ___17/3/16_____