STRIDER

A Randomised Controlled Trial of Sildenafil therapy In Dismal Prognosis early-Onset Intrauterine Growth Restriction

2013-005398-32

Independent Safety and Data Monitoring Committee (ISDMC) Charter

Contents

1 INTRODUCTION

1.1 Main Objectives of the Trial[1] and Trial Design

Primary Outcome:
Primary outcome is randomisation to birth interval. One week difference in the mean randomisation to birth interval is considered to be clinically important.

Secondary Outcomes:

Fetal outcomes include:

i. Estimated fetal weight
ii. Abdominal circumference growth velocity
iii. Serial measurements of Doppler pulsatility index in the umbilical artery, middle cerebral artery and ductusvenosus and uterine arteries
iv. Serial measurements of short term variability of the fetal heart rate recorded by transabdominalcardiotocography

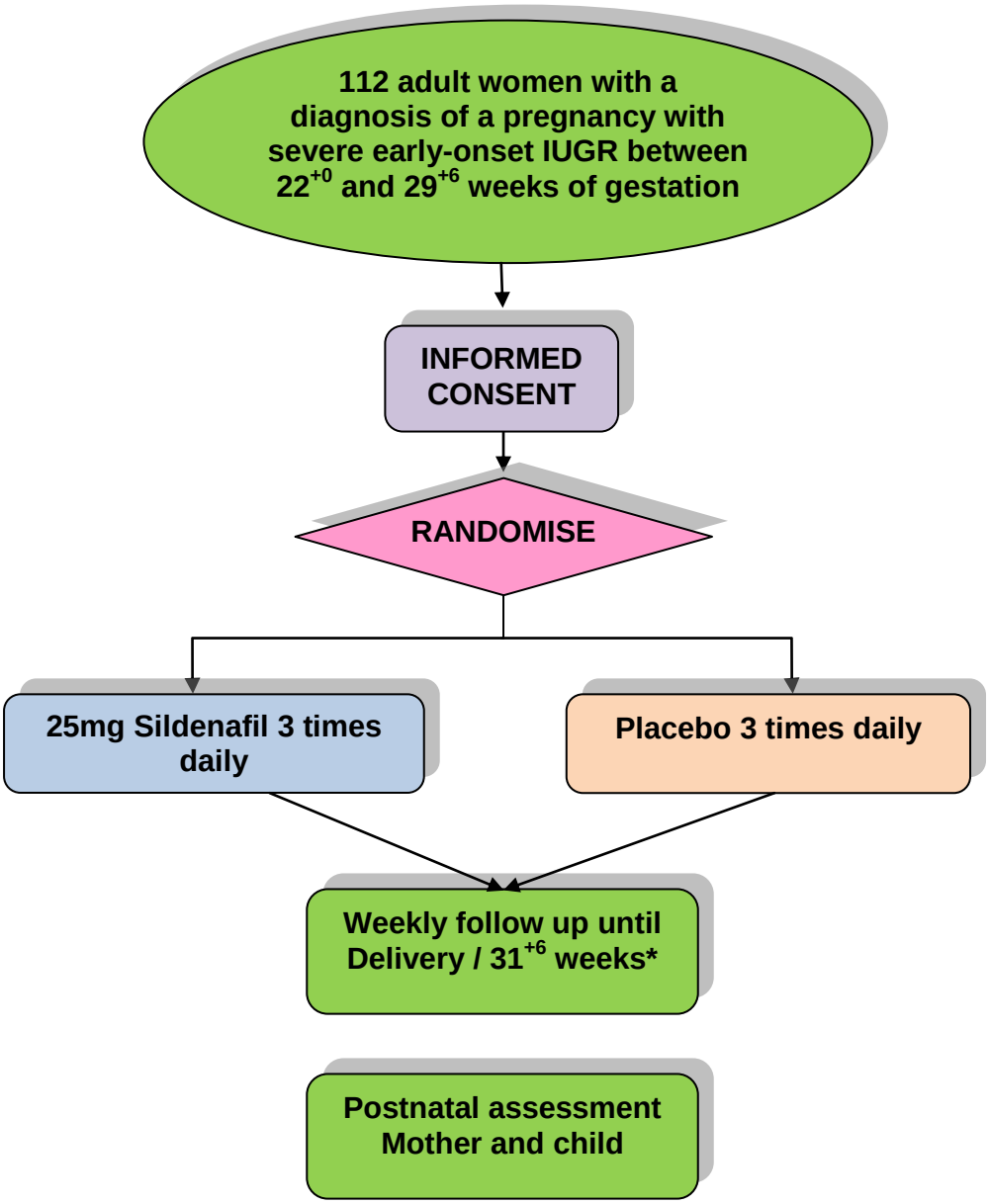
Infant outcomes include:

I. Gestational age at birth
II. Survival to discharge
III. Birth weight centile
IV. Length of admission on the Neonatal Intensive Care Unit
V. Oxygen dependency at day 28 and 36 weeks corrected age
VI. Necrotising enterocolitis
VII. Retinopathy of prematurity
VIII. Significant (grade III/IV) cerebral haemorrhage detected by cerebral ultrasound.
IX. Number of doses of surfactant
X. Ventilator days
XI. Supplemental oxygen days
XII. Number of days to full feeds

Maternal safety monitoring include:

I. Mode of delivery
II. Standardised blood pressure and pulse monitoring during treatment
III. Pre-eclampsia
IV. Postpartum haemorrhage
V. Recording of the side effects e.g. headache, fatal flushing
VI. In-patient postnatal stay

[1] The term 'Trial' includes all clinical studies for in order to maintain familiar terminology



1.2 Scope of ISDMC Charter

This ISDMC charter defines the roles and responsibilities of the Independent Safety and Data Monitoring Committee (ISDMC) for the STRIDER trial, explains the ISDMC's relationship with other trial committees, provides details of the ISDMC membership and describes the purpose and frequency of its meetings. This charter also describes the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the ISDMC, and an outline of the content of the Open and Closed Reports that will be provided to the ISDMC for each meeting.

2 ROLES AND RESPONSIBILITIES

2.1 General Responsibilities

The ISDMC is responsible for safeguarding the interests of the STRIDER participants, assessing the safety and efficacy of the interventions during the trial.

The ISDMC should receive and review the progress and accruing data of this trial and make recommendations to the Trial Steering Committee (TSC) on whether there are ethical or safety reasons why the trial should not continue. The ISDMC will be advisory to the TSC. The TSC will be responsible for promptly reviewing the ISDMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

To undertake interim review of the trial progress by:

- assessing data quality, including completeness
- monitoring recruitment figures and losses to follow-up
- monitoring compliance with the protocol by participants and investigators
- monitoring evidence for treatment differences in the safety outcome measures and thus recommending action when/whether the main trial question has been answered
- monitoring evidence for treatment harm e.g. toxicity, SAEs, deaths
- recommending whether the trial should continue to recruit or follow-up [see section on decision-making]
- monitoring planned sample size assumptions
- requesting additional data analyses for monitoring purposes of the ISDMC
- assessing the impact and relevance of any external evidence provided
- monitoring compliance with previous ISDMC recommendations
- considering the ethical implications of any recommendations made by the ISDMC
- To review the annual Development Safety Update Report
- Considering the need for interim analysis advising the TSC regarding the release of data and/or information
- Considering data emerging from other related studies if asked by the TSC, Sponsor or Funder

It is not the role of the ISDMC to change the planned sample size of the trial. In the event that an internal pilot has been built into the trial the ISDMC may be asked to consider whether the parameters used in the sample size calculation were reasonable and feed their comments back to the TSC.

2.2 Specific Roles of the ISDMC

The ISDMC chair (or vice-chair, in their absence) is expected to facilitate and summarise discussions. The ISDMC statistician will provide independent statistical expertise and to further guide other ISDMC members through the report. The ISDMC statistician is not expected to prepare the ISDMC report. The ISDMC clinician will provide independent clinical expertise.

3 MEMBERSHIP OF THE ISDMC

3.1 ISDMC Members

The ISDMC is an independent (should not be involved with the trial in any other way or have some competing interest that could impact on the trial) multidisciplinary group consisting of at least one statistician and at least one clinician that, collectively, have experience in the management of Fetal Medicine and in the conduct of randomised clinical trials.

Members of the ISDMC for the STRIDER trial are

ISDMC Statistician: **Ed Juszczak**

chairperson **Director NPEU Clinical Trials Unit**
National Perinatal Epidemiology Unit
Nuffield Department of population
Health University of Oxford
Old Road Campus
Headington
Oxford
OX3 7LF
Tel: 01865 289743
Email: ed.juszczak@npeu.ox.ac.uk

ISDMC Clinician: **Christoph Lees**
Consultant Obstetrician and Subspecialist in Fetal Maternal Medicine
Imperial College Healthcare NHS Trust
Tel/Fax:
Email: christoph.lees@imperial.nhs.uk

ISDMC: **Ben Stenson**
Consultant Neonatologist, Senior Lecturer Neonatal Unit
Simpson Centre for Reproductive Health
Royal Infirmary of Edinburgh
EH16 4SA
Tel/Fax: 01312422599
Email: ben.stenson@nhslothian.scot.nhs.uk

3.2 Membership and Conflicts of Interest

The ISDMC membership of the STRIDER trial has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Involvement in other trials or intellectual investment could be relevant. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the ISDMC. Members must sign an ISDMC member's disclosure agreement and confidentiality agreement (Section 10), which states that members do not have any conflicts of interest and that all information discussed within the closed reports will remain confidential. Any concerns the ISDMC may have should be communicated to the TSC directly.

Any ISDMC member who develops significant conflicts of interest during the course of the trial should resign from the ISDMC.
ISDMC membership is for the duration of the clinical trial. If any members leave the ISDMC during the course of the trial, the STRIDER Trial Coordinator in consultation with the TMG and TSC will promptly appoint their replacements.

3.3 Indemnity

The ISDMC membership has indemnity coverage via the University of Liverpool's Professional Indemnity insurance. This is in the event of the ISDMC being sued by a trial participant (or family member) for example.

4 ORGANISATION OF ISDMC MEETINGS

4.1 Format of Meetings

ISDMC meetings will be arranged by the STRIDER Trial Coordinator on a date suitable for all members to attend. If, at short notice, any ISDMC members cannot attend at all then the ISDMC may still meet if at least one statistician and one clinician, including the Chair or Vice-Chair (unless otherwise agreed), will be present.

ISDMC meetings will either be face-to-face or by teleconference.

To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for Open Sessions and Closed Sessions will be implemented. The intent of this format is to enable the ISDMC to preserve confidentiality of the comparative safety and efficacy results while at the same time providing opportunities for interaction between the ISDMC and others who have valuable insights into trial-related issues.

In the case of a teleconference, the call for the open session must be ended and restarted for the closed session.

A representative of the TMG (typically the Trial Co-ordinator) shall prepare standard agenda and a study summary for each meeting including recruitment figures, status of sites and details of any issues. The Trial Statistician will prepare open and closed reports in agreement with the DMC.

4.2 Open Session

An open session between the ISDMC members, the Trial Statistician, Chief Investigator and an appropriate member of the TMG will be held before the closed session. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved. The open report will be reviewed during the open session.

4.3 Closed Session

Closed sessions involving only ISDMC membership and the trial statistical team who generated the closed reports will be held to allow discussion of confidential data from the clinical trial, including information about the relative safety of interventions.
At the end of each closed session, the ISDMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue. The closed report will be reviewed during the closed sessions.

4.4 Initial ISDMC Meeting

The initial ISDMC meeting should be held face-to-face if possible. At the first meeting, members will be provided with a copy of the clinical trial protocol and patient information a copy of this ISDMC charter and a copy of the template ISDMC report for review and approval.

The relevant signature pages must be completed prior to, or at the start of the meeting.

The ISDMC will decide whether they will be unblinded in their assessment of safety data and on the frequency of future ISDMC meetings. Members will also decide how far in advance of future meetings they wish to receive open and closed reports and any supporting documentation at least once a week.

The frequency of subsequent ISDMC meetings will be decided at the initial meeting and the procedure for minute taking will also be confirmed.

4.5 Scheduled and Unscheduled ISDMC Meetings

The frequency of ISDMC meetings will be decided at the initial meeting (and noted in the minutes) but will be at least annual. Typically, the ISDMC will meet shortly before the TSC are scheduled to meet although there may be periods when more frequent meetings are necessary.

Major trial issues may need to be dealt with between meetings, by phone or by email. ISDMC members should be prepared for such instances. The ISDMC Chairperson should decide whether an unscheduled meeting should be held and such meetings will be organised by the TMG (unless otherwise specified by the Sponsor).

4.6 Formal Interim Analysis & Stopping Rules

Exact criteria for “proof beyond reasonable doubt” are not, and cannot be, specified by a predefined stopping rule. The DMC charter is in accordance with the Peto-haybittle stopping rule whereby an interim analysis of major endpoints would need to involve a difference between treatment and placebo of at least three standard errors to justify premature closure. Interim subgroup analysis would need an even greater burden of evidence to justify premature closure. The number and timing of interim analyses is not predetermined. In summary, the stopping rules require extreme differences to be present to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgement.

The main analyses will compare all those allocated sildenafil versus those allocated placebo, on an ‘intention to treat’ basis, irrespective of whether they received the allocated treatment or not. Results will be presented as appropriate effect estimates with a measure of precision (95% confidence intervals). Frequency and nature of interim analyses including safety analysis will be determined in discussion with DMC and recorded in DMC report plan.

Detailed statistical plan will be developed before the trial database is locked for interim analysis. It is important that the SAP is written blind to emerging results. The plan will include adjustments for randomised strata (centres, gestation) and subgroup analysis. Interaction test will be used to test whether the effect of treatment (if any) differs across these subgroups.
Analysis will be performed at the LCTU by the trial statistician.

A draft statistical report will be prepared in accordance with the relevant LCTU SOPs and submitted to the ISDMC for approval.

4.7 Final Study Meeting

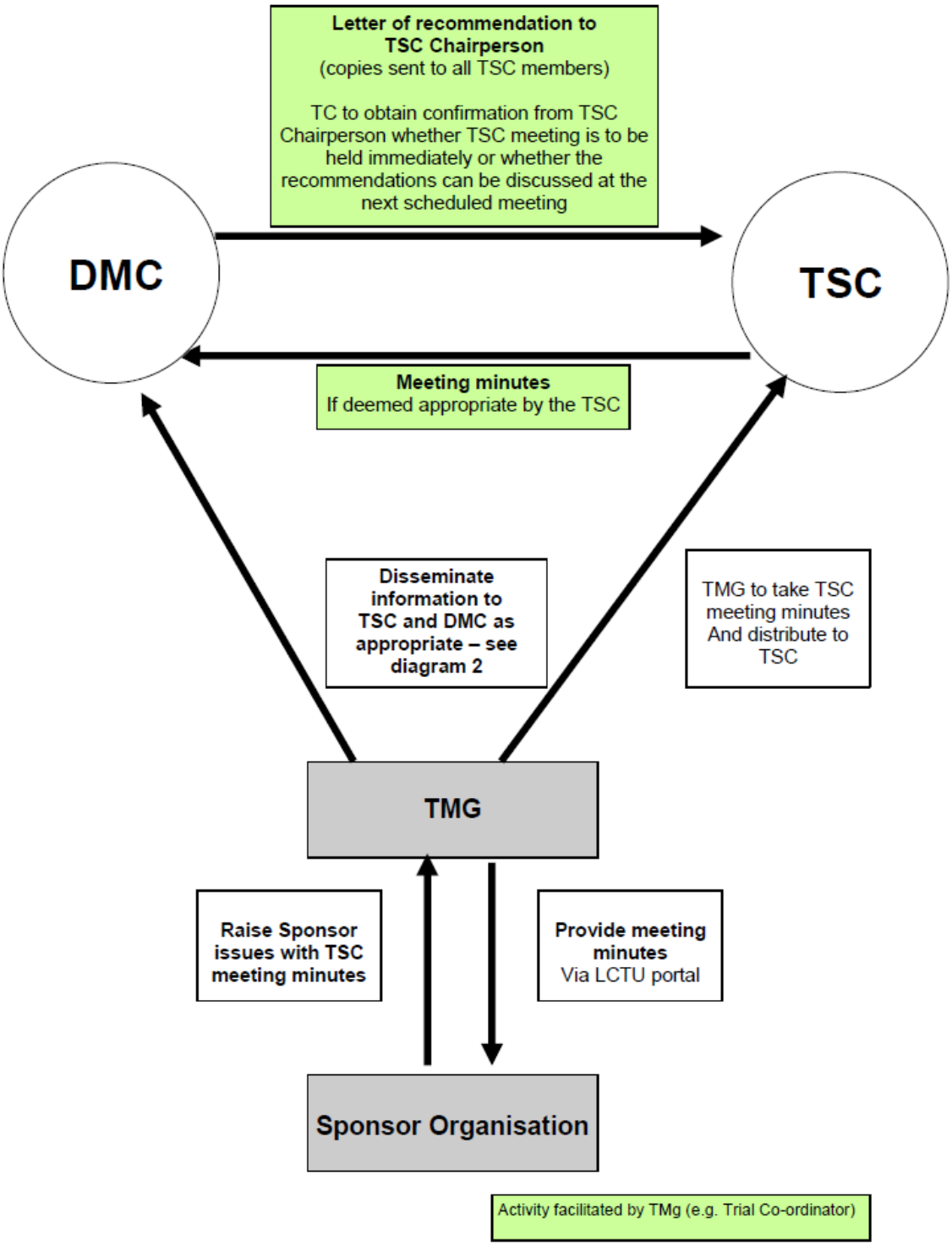
Final analysis of the primary and secondary outcome measures will be carried out at study closure or after a sufficient follow-up and event rate have been achieved. A final study meeting will preferably be held in person upon the availability of the final study analysis. If the study is terminated based on the recommendations of the ISDMC, no final study meeting is required.

5 COMMUNICATION WITH THE TSC, TMG AND SPONSOR

The ISDMC should ensure that appropriate efforts are made to ensure that relevant discussions are adequately disseminated by the TMG and that due consideration is given to how decisions will be implemented by the TMG.

Diagrams 1 and 2 below show the process for communication between the TSC and the TMG, trial oversight committees and the Sponsor.

Diagram 1:
Communication diagram for disseminating discussions from Trial Oversight Committee meetings



6 RECOMMENDATIONS AND DECISION MAKING

6.1 Final Study Meeting

The ISDMC is advisory to the TSC and should therefore generate recommendations at the end of each ISDMC meeting.
The possible recommendations are numerous and could include:

- No action needed, trial continues as planned in accordance with the current protocol
- Early stopping due to, amongst other things, safety concerns, futility, slow recruitment, or external evidence
- Stopping recruitment within a subgroup
- Extension of recruitment or follow-up
- Stopping one of the treatment arms
- Advising on or proposing protocol changes

The ISDMC will make a recommendation on the target sample size of the trial if an internal pilot has been undertaken.

These should be reported to the TSC as described in section 8.1.

6.2 Achieving Consensus

Every effort should be made to achieve consensus between the ISDMC members and this should be facilitated by the Chairperson (or, in their absence, the Vice-Chair). It is important that all potential implications are considered before a final decision is made. In each area of discussion, the Chairperson (or Vice-Chair) should give their own opinion last.

If a consensus cannot be reached, the decision will be put to a vote.

6.3 Voting

All three ISDMC members are eligible to vote. Details of the vote should not be routinely included in the report to the TSC, as it may inappropriately convey information about the state of the trial data.

If the ISDMC is considering recommending major action the ISDMC Chair (or Vice-Chair) should talk with the absent members as soon as possible after the meeting to check they agree. If they do not, a further teleconference should be arranged with the full ISDMC.

7 DOCUMENTATION OF ISDMC MEETINGS

7.1 Minutes of ISDMC Meetings

Two sets of meeting minutes will be prepared: open session minutes and closed session minutes.

A representative of the TMG will normally take minutes of the open session of ISDMC meetings but this should be decided at the initial ISDMC meeting. A summary of the main points discussed should be clearly detailed.

The Trial Statistician will typically take the minutes of the closed session of ISDMC meetings but this should be decided at the initial ISDMC meeting.

The closed minutes will detail the discussions from the closed sessions of the ISDMC meeting, including the listing of all of the recommendations by the ISDMC.

As it is likely these minutes may contain unblinded information; it is important that they are not made available to anyone outside the ISDMC.

Copies of the minutes from the closed session must be kept by the trial statistician for distribution to the sponsor, lead investigators and regulatory authorities at the time of study closure, if necessary. Selected comments from the closed minutes may be forwarded to the TMG for them to action, if appropriate as agreed by the chair.

All appropriate members of the ISDMC should review the open and closed meeting minutes. If no comments are returned within 2 weeks of sending out the draft minutes, it will assumed that the attendee has no comments and is happy with the draft minutes. Following the 2 weeks period, the minutes should be finalised and sent to all attendees and non-attendees for information. The ISDMC Chair needs to approve to the minutes.

8 COMMUNICATION WITH THE TSC, TMG AND SPONSOR

Diagrams 1 and 2 show the process for communication between the ISDMC and TSC, as well as the TMG and Sponsor.

Diagram 1:
Communication diagram for disseminating discussions from Trial Oversight Committee meetings

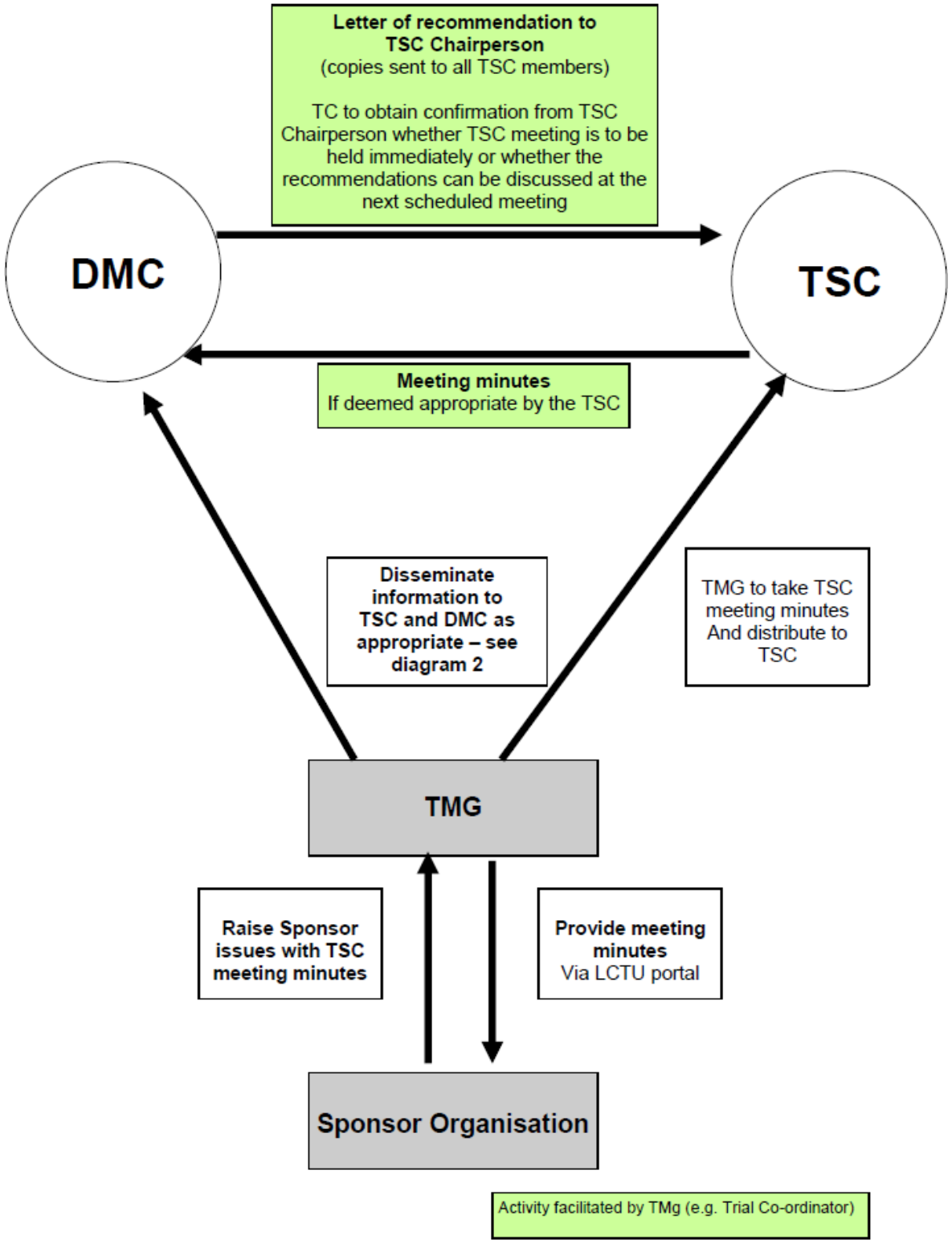
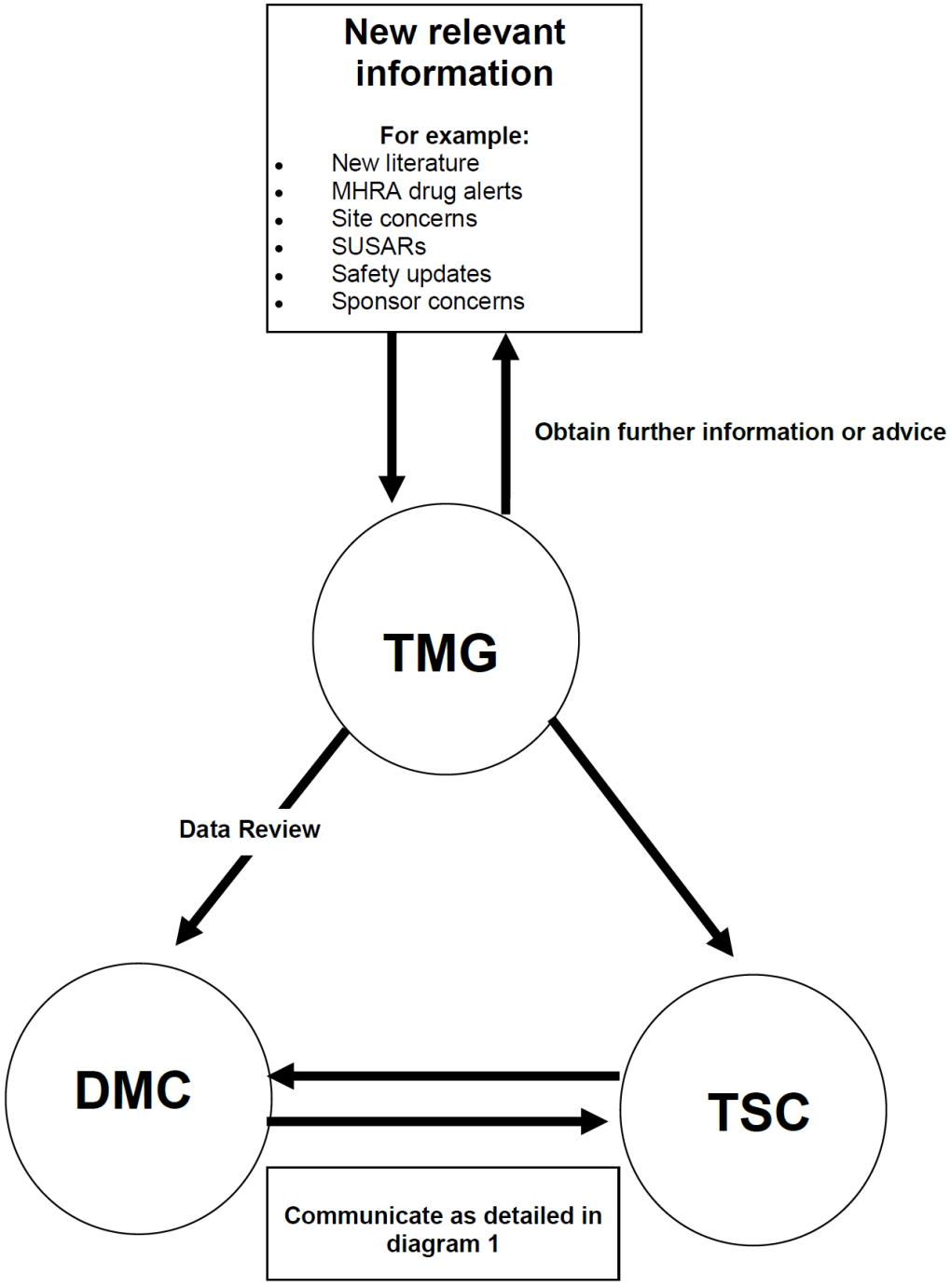


Diagram 2:
Communication diagram for disseminating new relevant information identified outside of Trial Oversight Committee meetings



8.1 Reporting to the TSC

The ISDMC should report their recommendations (see section 6.1) in writing (i.e. send a 'letter of recommendation') to the TSC, usually within 3 weeks after the meeting. This is a separate document to the ISDMC minutes which may be prepared by the TMG for the ISDMC Chair to

review. The TMG may also assist the sending of the finalised, signed letter of recommendation to the TSC. An electronic version is acceptable.

Unless the ISDMC is recommending that the trial protocol be changed in some way, the letter to the TSC should not usually reveal any confidential information.

Additionally, the letter should be copied to the Chief Investigator, although their copies should have any confidential information (i.e. comments on data by group on the main outcome measures) removed, and noted as such.

8.2 Reporting to the Sponsor

The TMG shall provide final meeting minutes of the open sessions and a copy of the letter of recommendation to the Sponsor via the LCTU portal (see diagram 1).

If the Sponsor raises any concerns with the ISDMC discussions these will be relayed to the ISDMC via the TMG.

8.3 Disagreement between ISDMC and TSC

The TSC has ultimate responsibility for the trial. However, the TSC should report to ISDMC how they have acted upon the ISDMC recommendations. If the ISDMC has serious problems or concerns with the TSC decision, a meeting of these groups should be held.

The information to be shown would depend upon the action proposed and the ISDMC concerns. The meeting should be chaired by a senior member of the LCTU or an external expert who is not directly involved with the trial. Depending on the reason for the disagreement confidential data may have to be revealed to all those attending such a meeting.

9 DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

The trial coordinator will compile the DSUR with the aid of the Chief Investigator, where appropriate, and in the case of blinded studies another trial coordinator will compile the safety data for the report.
The DSUR will then be sent to the chair of the ISDMC for review. They may alter the report in discussion with the CI and trial coordinator. The chair should approve the final version prior to submission to the MHRA. Approval can be given via email. If the chair is absent when the DSUR is due for submission then this task can be delegated to the Vice-Chair or Independent Clinician.

10 AFTER THE TRIAL

10.1 Publication of Results

The Chief Investigator has responsibility for ensuring that trial results will be published in a correct and timely manner. The TSC is the committee that should oversee this process.

10.2 Information about the ISDMC to be included in trial reports

ISDMC members will be named (unless they specifically ask not to be) in the primary published report. A brief summary of the timings and conclusions of ISDMC meetings should be included in the body of this paper.

10.3 ISDMC approval of publications

The ISDMC members should be given at least two weeks, and if possible a month, to read and comment on any draft publications that report outcome measures and/or details of the ISDMC. This may be done simultaneously with other groups reviewing the draft manuscript (e.g. TSC, trial investigators).

10.4 ISDMC constraints for divulging information

The ISDMC should not discuss confidential issues from their involvement in the trial until 12 months after the primary trial results have been published, unless permission is agreed with the TSC. They should not trade in stock of companies affected by the trial until the results are public knowledge. See sections 3.2 and 10.1.

11 STRIDER SIGNATURE PAGES

Each ISDMC member should complete, SIGN and DATE two copies of the Charter Signature Page (section 11.1). One copy should be returned to:

Trial Coordinator
Sarah Quinby
Cancer Research UK Liverpool Cancer Trials Unit
1st Floor, Block C
Waterhouse Building
1-3 Brownlow Street
Liverpool
L69 3GL

11.1 STRIDER ISDMC Charter Signature Page VERSION 2.0 16th June 2015

I confirm that:

11.1.1. I have read this Charter, I understand it, and I will work according to it.

11.1.2. I will work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable laws and regulations.

11.1.3. I have no significant conflicts of interest to declare. The source of these conflicts may be financial, scientific or regulatory in nature.

11.1.4. I am not involved in any other trial or intellectual investment that could be relevant. I confirm that I will not trade in stock of companies affected by the trial until the results are public knowledge.

11.1.5. I do not have regulatory responsibilities for the trial products.

11.1.6. If I develop any significant conflicts of interest during the course of the trial I should resign from the ISDMC.

11.1.7. I agree to keep in confidence all information generated as result of or related to the trial, including without limitation safety data, study observations, study progress and relations to third parties, including regulatory authorities and ethical committees. The undertaking and obligation to maintain confidentiality shall survive by five years. This provision shall not preclude either the member or institutions from informing third parties about member's membership of the committee.

11.1.8. My obligation to maintain confidentiality as set out in clause 11.1.7. shall not apply to communications between or among Committee members, Committee members and Institutions directors and/or officers, and/or – at the request of Institutions – Committee members and regulatory authorities or other relevant third parties authorised by Institutions, provided that the Committee members in any communication with any regulatory authority or authorised third party shall instruct the authority or the third party to maintain confidentiality to the extent permitted by law.

11.1.9 The obligation to maintain confidentiality as set out in clause 11.1.7. shall not apply to information, which by other interests than the recipient, and without the recipient disclosing any information to such interests, has been:

a) made generally available to the public by third parties or the disclosing party;

b) published by or with the consent of the disclosing party, e.g. by publication in scientific periodicals or at meetings, seminars or symposiums;

c) made available to the public by a third party who did not acquire directly or indirectly the information from the Member and/or Institutions;

d) required by any law, rule, regulation, decision, order, subpoena or other process to be disclosed. If such disclosure is requested, the party receiving such a request will promptly notify the other party of such request.

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Signature of Committee Member Date

_____

Committee Member Name (print or type)

_____

Committee Member Role

_____

Name of Institution

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Location of Institution (City, Country)