DMC CHARTER Dutch STRIDER STUDY

1. INTRODUCTION	
Name (and sponsor's ID) of trial plus ISRCTN and/or EUDRACT number	Dutch STRIDER (ZonMW 80-83600-98-20081) (Eudract 2012-004112-63)
Objectives of trial, including interventions being investigated	To evaluate the effectiveness of sildenafil (versus placebo) in achieving healthy perinatal survival.
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent DMC for the Dutch STRIDER, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.
2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the committee	To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.
Terms of reference	The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Principle Investigator of the trial. The DMC should inform the Principle Investigator if, in their viewthe results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management.
Specific roles of DMC	Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. • monitoring evidence for treatment differences in the main efficacy outcome measures • monitor evidence for treatment harm (Sildenafil) • decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone advise on protocol modifications suggested by investigators or sponsors (eg to inclusion criteria, trial endpoints) • advise on protocol modifications suggested by investigators or sponsors (eg to inclusion criteria, trial endpoints) • considering the ethical implications of any recommendations made by the DMC • assess the impact and relevance of external evidence provided by the research group
3. BEFORE OR EARLY IN THE TRIAL	
Any issues specific to the disease under study	All DMC members will have sight of the protocol before agreeing to join the committee The DMC members are specifically asked to comment on the monitoring plan and interim analyses planned.
Whether the DMC will meet before the start of the trial	The DMC does not meet before start of the trial, but will have insight in the study protocol and may suggest protocol changes before start of the trial. Within six months after start of the trial the study will be presented to a open DMC meeting.
Any other issues specific to the treatment under study	None
Any specific regulatory issues	None

Whether members of the DMC will have a contract	There will be no contract. The DMC members will sign a 'no conflict of interest statement', on this form they also state to have read this charter and agree to be member of the DMC.
4. COMPOSITION	
Membership and size of the DMC	The members of the DMC for this trial are: *(1) prof. dr. J.G.P. Tijssen, MD, PhD - statistician (chair)* Professor Tijssen is specialist in clinical epidemiology of cardiovascular diseases. He has served on many DSMB's in multiple fields of medicine. (2) *prof. dr. F.M. Helmerhorst, MD, PhD – gynaecologist LUMC* Professor Helmerhorst is gynaecologist in the LUMC, his specialty is clinical epidemiology of reproductive medicine, and focuses on the balance between effects and side-effects. (3) *prof. dr. M.P.M. Burger, MD, PhD – gynaecologist AMC* Professor Burger is a gynaecologist in the AMC, he is general gynaecologist with oncology and epidemiology as specialty. (4) dr. J.H. van der Lee, MD, PhD – epidemiologist AMC Doctor van der Lee is specialist in epidemiological research in general practice and pediatrics, at the division 'Vrouw en Kind' at the Academic Medical Center. Her main interests are clinimetrics of health outcomes in RCTs and RCT methodology related to optimal sample sizes and Data Monitoring Committees. (5) Dr. D.P van der Ham – gynaecologist, Martini Ziekenhuis Dr. van der Ham is gynaecologist in the Martini Ziekenhuis. He has experience with running a large multicentre trial in obstetrics, the PPROMEXIL trial. (6) Dr. T.R. de Haan. – neonatologist, AMC. Doctor de Haan is neonatologist in the AMC and his main interests are neurology and brain imaging in neonatology.
The Chair, how they are chosen and the Chair's role.	Prof. dr. J.G.P. Tijssen is Chair, he has served in several DMC's before in this role. He is Chair of the DMC for multiple consortium studies, chosen based on his expertise in statistics, especially trials and interim analysis.
The responsibilities of the DMC statistician	The statistician is Chair of the committee, will attend all meetings; will provide statistical advice and recommendations. The statistician/chair will also summarize the meetings.
The responsibilities of the trial methodologist	The trial methodologist C.A. Naaktgeboren will oversee the production of the report to the DMC. An independent methodologist dr. M. Van Wely will produce the report. The trial methodologist will provide any additional information if needed by the DMC.
The responsibilities of the trial office team	The principle investigator and coordinating researcher only inputs to the production of the non-confidential sections of the DMC report.
The responsibilities of the PI and other members of the Trial Management Group (TMG)	The PI, may be asked, and should be available, to attend open sessions of the DMC meeting. The other TMG members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of DMC Meetings).
5. RELATIONSHIPS	
Relationships	The study group is responsible for planning and the conduction of the trial and is backed by the Consortium Board. The DMC will be the independent committee safeguarding the patients. The medical ethical committee will approve the trials before starting.
Clarification of whether the DMC	The DMC plays an advisory role. If the advice of the DMC will be

are advisory (make recommendations) or executive (make decisions)	neglected or overruled, the medical ethical committee will be informed.
Payments to DMC members	DMC members will be reimbursed for travel expenses.
The need for DMC members to disclose information about any competing interests	All competing interests will be disclosed at the first DMC meeting.
6. ORGANISATION OF DMC MEETINGS	
Expected frequency of DMC meetings	The DMC will meet for an interim analysis on safety parameters (neonatal mortality and morbidity) will be performed for the first 177 cases, with a p <.01 (modified Haybittle Peto alpha spending rule) and an extra meeting will be planned if indicated by the number or kind of SAEs.
Whether meetings will be face-to-face or by teleconference	In principle the meetings will be face-to-face. Additional teleconference meetings can be planned if indicated.
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	The face-to-face meetings of the DMC will consist of an open and a closed session. The first meeting of the DMC will be open, with a presentation by the coordinating researcher and in presence of the principal investigator of the trial and the trial methodologist. After this meeting a closed session will be planned. Further meetings will be closed; if necessary the trial methodologist will be present.
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Intended content of material to be available in open sessions	Open session: The protocol will be explained and clarified in the first session. Accumulating information relating to recruitment and data quality (eg data return rates, treatment compliance) will be presented. Total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.
Intended content of material to be available in closed sessions	Closed sessions: In addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group as described in the protocol.
Will the DMC be blinded to the treatment allocation	The DMC will be blinded, but can be unblinded by the independent methodologist on request without any further clarification. This request will be granted in all cases, it will be noted by the independent methodologist.
Who will see the accumulating data and interim analysis	The accumulating data on safety and efficacy will be seen by the independent methodologist and all DMC members only. The study group will have insight into the total number of (serious) adverse events, also divided by group, but will not have insight in the efficacy data. DMC members do **not** have the right to share confidential information with anyone outside the DMC, including the PI.
Who will be responsible for identifying and circulating external evidence (eg from other trials/ systematic reviews)	The coordinating researcher will be responsible for identifying and circulating external evidence.
To whom the DMC will communicate the decisions/ recommendations that are reached	Decisions or recommendations that are reached will be communicated to the principal investigator of the study (dr. J.W. Ganzevoort), and the trial office of studies in Obstetrics and Gynaecology (info@studies-obsgyn.nl). To ascertain timely decisions, this will be done within 3 weeks after the DMC meeting, or the trial office will be informed that more time is required.
Whether reports to the DMC be	Upfront the first meeting the protocol and other relevant material

available before the meeting or only at/during the meeting	related to the trial will be sent to the DMC, this is planned to be sent 3-4 weeks upfront the meeting. Interim analysis data will be sent to the chair of the DMC, the chair may decide whether a face-to-face meeting is required, or the decision can be made by a telephone conference.
What will happen to the confidential papers after the meeting	The DMC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMC members should destroy all interim reports. The trial statistician should monitor that after the trial is reported, important interim analysis data is gathered from the independent statistician and kept confidently by the (institute) of either the principal investigator or by the study coordinator.
8. DECISION MAKING	
What decisions/recommendations will be open to the DMC	Possible recommendations could include: • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment or external evidence • Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up • Stopping recruitment within a subgroup • Sanctioning and/or proposing protocol changes
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	For this trial we plan to monitor safety after the inclusion of each 50 women. The DSMB may decide to alter the frequency of these safety checks as needed. Accumulating data on serious adverse events will be send to the DSMB at a predetermined number of events for safety review. For this trial we will send data on every maternal severe adverse event. For this trial we plan an interim analysis for efficacy which will be performed after inclusion of the first 177 women. The trial will be stopped when at interim analysis a signficant difference between the two treatment arms is be observed ($p<0.01$ according to the modified Haybittle Peto alpha spending rule). These interim analysis are specified in the protocol page 26. These interim-analysis can also include data from other ongoing trials. Within the prospective IPD-effort designed and agreed upon by similar STRIDER-trials in Australia/New Zealand, United Kingdom, Ireland and New Zealand, emerging evidence may come up and be presented to the umbrella DSMB of these studies. From each national study, one member will also take seat in the international DSMB. The international DSMB is in the position to advise the national DSMB on the abovementioned actions. The National DSMB is independent and has its own autonomy to come to decision for the national trial. These methods will be used as a guideline. Regardless of the p-values, the DSMB can advise to stop the trial at any moment when the safety of the patients is considered to be in danger. These reasons should be noted. When the principal investigator deviates from the advice from the DSC, this will be reported to the METC.
How decisions or recommendations will be reached	Every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken,

within the DMC	although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made.
When the DMC is quorate for decision-making	Effort should be made for all members to attend. The trials office team will try to ensure that a date is chosen to enable this, therefore 4 face-to-face meetings are planned in advance in January. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed) will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should inform the absent members as soon after the meeting as possible to check they agree. If they do not, a teleconference should be arranged with the full DMC.
Can DMC members who cannot attend the meeting input	If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC Chair for consideration during the discussions.
What happens to members who do not attend meetings	If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.
Whether different weight will be given to different endpoints (e.g. safety/efficacy)	Safety of participants will be most important.
Any specific issues relating to the trial design that might influence the proceedings, e.g. cluster trials, equivalence trials, multi-arm trials	N.A.
9. REPORTING	
To whom will the DMC report their recommendations/decisions, and in what form	Decisions will be communicated by a formal letter to the PI through the trial bureau, within 3 weeks, with cc to the independent statistician who performed the interim analysis or the trial statistician. If no safety issues are identified, this will also be confirmed by letter.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Notes of the meeting will be made by Christiana Naaktgeboren, trial office staff member. If she cannot be present, she will point someone else to this task. They will be checked by the Chair of the DMC. Minutes of the closed session of the meeting will be made by Dr van der Lee
What will be done if there is disagreement between the DMC and the body to which it reports	If the DMC has serious problems or concerns with the decision of the principal investigator, a meeting of the trial coordinating team and the DMC should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial.
10. AFTER THE TRIAL	
Publication of the results	The trial protocol will state that results will be published in a correct and timely matter. The DMC will not standard provide input for the publication, but they may give advice about data interpretation if they consider it necessary, or based on questions from the principal

	investigator. The consortium also has a methodological advice committee, which can be consulted for these issues.
The information about the DMC that will be included in published trial reports	DMC members will be named and their affiliations listed in the acknowledgements of the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings will be included in the main trial manuscript.
Any constraints on DMC members divulging information about their deliberations after the trial has been published	The DMC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published, or otherwise when permission is agreed with the overseeing committee.

Annex 1: Suggested letter from DMC to principal investigator.

J.W. Ganzevoort
Meibergdreef 9
Room H4-278
1105 AZ Amsterdam

<date>

Dear J.W. Ganzevoort

The Data Safety Monitoring Board of the Dutch STRIDER trial has recently conducted <safety review/ interim analysis?> for this RCT. <Members present atmeeting> have reviewed outcomes (specify outcomes) reported before <date>.

Based on this review, we would like to state that the review did not raise specific safety concerns for the Dutch STRIDER trial. Therefore, the Dutch STRIDER trial should proceed according to protocol.

We shall next review the progress and data <provide approximate timing>.

With kind regards,

also on behalf of the other members of the DSMB, professors F. Helmerhorst (gynaecologist) and M Burger (gynaecologist), J. van der Lee (epidemiologist), D. van Der Ham (gynaecologist) and T.R. de Haan (neonatologist).

Jan G.P. Tijssen, Chair Dutch STRIDER DSMB

eCC: F. Helmerhorst, M. Burger (DSMB)
eCC: <independent statistician>

Potential conflict of interest form for Data Monitoring Committee members for the Dutch STRIDER trial.

Principal investigator: J.W. Ganzevoort
Sponsor name: ZonMW
Financial support of trial: ZonMW

This form should be completed during the installment of the DMC for this trial Dutch STRIDER

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.

All possible competing interests should be disclosed during the first meeting of the DMC, when the DMC is installed for the trial. If the conflict of interest is considered substantial, the potential DMC member should remove the conflict or stop participating in the DMC.

As potential competing interests we consider:

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by the trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict, e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following two questions and return the form to the trials office.

1. Do you have any competing interest for being DMC member for the Dutch STRIDER?

☐ No, I have no competing interests to declare.
☐ Yes, I have competing interests to declare, details:

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2. Do you agree to be a member of the DMC for the Dutch STRIDER

- ☐ I have considered my potential conflicts of interests and declare to be member of the DMC of the Dutch STRIDER, and accept the associated roles and responsibilities as described in the DMC charter.

Name: _____

Signature: _____

Date: _____/_____/_____ [dd/mm/yyyy]