Data and Safety Monitoring Board (DSMB)

Charter

OPTION – OutPatienT InductiON

Labour induction in an outpatient setting - a multicenter randomized controlled trial

C o n f i d e n t i a l

Name of Sponsor:	Verena Sengpiel/Ylva Carlsson – the steering committee for OPTION
ClinicalTrials.gov ID:	< Clinicaltrials.gov ID>
Protocol Number:	Vs 1
Contacts at Sponsor:	As Applicable: Verena Sengpiel, MD, Associate Professor, Ylva Carlsson MD, Post Doc, Department of Obstetrics and Gynecology, Sahlgrenska University Hospital and Sahlgrenska Academy, Gothenburg University <Name of Medical Monitor>
Date of Charter:	May 14th 2020

Confidential

Note: This Charter will serve as the Standard Operating Procedure (SOP) for the DSMB.

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1 INTRODUCTION

Purpose and aim: The Swedish induction of labour rate is about 20%. Due to recently published results showing decreased perinatal mortalityin case of induction at gestational week 41 instead of 42 weeks, an increase to about 30% of all pregnancies is expected. Induction is associated with longer stays at the hospital. It has been suggested that women could return home and be re-admitted at start of active labour, so-called outpatient induction. Outpatient induction has been shown to increase patient satisfaction and to save healthcare resources. However, even though outpatient induction is offered in clinical routine in many countries, e.g. Great Britain, Danmark and Finland, safety and efficacy have not been established. We aim to fill this knowledge gap by investigating safety, efficacy, acceptability and cost-effectiveness of outpatient compared to hospital induction in low-risk pregnancies.

Study design: A national, multicentre register-based randomised controlled trial utilising data from several registries in Sweden. Additional data will be collected using validated questionnaires and interviews.

Population: Low-risk women planned for induction (n=8891 in total and n=2119 in both groups (outpatient and hospital induction) and in both arms (Angusta/balloon catheter))

Intervention: Outpatient induction

Control: Hospital induction

Outcomes:

Primary: A composite outcome of severe neonatal morbidity or mortality

Secondary: Efficacy (vaginal delivery); further neonatal and maternal health outcomes the woman's, partner's and caregiver's experience; economics; future pregnancy outcomes

Impact: If safety and efficacy can be established, outpatient induction has the potential to increase patient satisfaction while contributing to a better use of healthcare resources.

For further information about the study please refer to the study protocol.

An independent Data and Safety Monitoring Board (DSMB) has been convened to assess the the safety data of this clinical study and critical safety end points and provide recommendations to the sponsor. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The DSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and data integrity of the study. This Charter will outline the roles and responsibilities and serve as the Standard Operating Procedure (SOP) for the DSMB of the OPTION trial (OutPatienT InductiON trial).

2 COMPOSITION OF THE DSMB

The Committee will be composed of 4 members (inclusive of the DSMB Chair). The DSMB includes experts in or representatives of the appropriate fields, such as obstetrics, pediatrics and statistics.

Members of the DSMB are:

1. Lars Ladfors, senior consultant and associate professor in obstetrics at Sahlgrenska University Hospital and Chair of DSMB
2. Göran Wennergren, Professor Emeritus in Pediatrics at Sahlgrenska University Hospital and co-chair
3. Mia Ahlberg, PhD, Head of midwifery science and development at Karolinska University Hospital
4. Fredrik Granath, Associate Professor at Karolinska University Hospital and biostatistician

The Chair is responsible for convening the DSMB. A meeting will take place at the interims-analysis (1000, 3500 and 6000) as well as at the finalization of the study. Additional meetings will also take place at extra-ordinary events related to a SAE. The chair will then convene for an extra session, hence the number of sessions during the study period for the DSMB depends on the number of SAEs and what kind of SAEs that happens. The SAEs will be presented to the DSMB blinded initially, but the DSMB will always have the right to know upon request which study arm the SAE has happened in.

Quorum – A quorum will occur when 3 members are present. Without a quorum a meeting will not be held, unless alternate arrangements have been made by the Chair in agreement with the sponsor that documents can be reviewed remotely and review comments will be provided to the Chair.

If a member misses a meeting, the Chair should ensure the member is available for the subsequent meeting. If a member misses a second meeting, the Chair should ask the member about his or her ability to remain on the DSMB. If a third meeting is missed, the member should be replaced. For planned interim analyses the Chair as well as the DSMB statistician must attend.

Each member will serve a term of 4 years. In case inclusion should not be achieved within 4 years DSMB members will be invited to remain in the DSMB until inclusion is completed. A member of the DSMB will be able to resign giving a three months notice. The sponsor will appoint a successer taking into account foremost that a specific competence will be replaced and secondly a geographical distribution within the group. The suggestion from the sponsor should be approved by the remainder of the DSMB.

3 INDEPENDENCE OF THE DSMB

It is essential that the judgment of members of the DSMB not be influenced by factors other than those necessary to maintain subject safety and to preserve the integrity of the study. Persons who have an apparent financial, intellectual, or other interests with a drug, device, or procedure should not be a DSMB participant for the evaluation of that product. Independence is essential to ensure that DSMB members are objective and capable of an unbiased assessment of the study's safety and efficacy data. The following will ensure the independence of the DSMB:

- Members of the DSMB will not participate as investigators in any study under review and will not be supervised by study investigators.

- Members of the DSMB must not have a direct interest in knowing or influencing trial outcome or have a financial or intellectual interest in the outcome of any studies under review.
- DSMB members must disclose all pharmaceutical companies, biotechnology companies, and clinical research organizations in which they hold financial interest. Members must disclose all consultancies (direct or indirect) with pharmaceutical companies, biotechnology companies, and clinical research organizations.
- Members who have served initially on protocol review teams may participate in the open sessions of the DSMB meeting when that protocol is under review. However, they will be excused from the closed sessions reviewing that protocol.

The sponsor will be responsible for deciding whether consultancies or the disclosed interests of the members materially affect their objectivity. Members of the DSMB will be responsible for notifying the DSMB Chair and the sponsor of any changes of interest in pharmaceutical companies, biotechnology companies, or clinical research organizations, including consultancies. In such cases, the DSMB meeting minutes will document the disclosure of the potential conflict of interest and the outcome of the discussion (e.g., abstention of member from voting, recusal from discussion). The sponsor will decide whether any of these relationships results in a conflict of interest which would preclude involvement on the DSMB. Members of the DSMB who develop potential or significant perceived conflicts of interest will be asked to resign from the DSMB. Members will be polled at the beginning of each DSMB meeting to disclose whether status has changed.

4 RESPONSIBILITIES OF THE DSMB

The DSMB is constituted only for a single protocol, hence DSMB members should only agree to serve if they are generally supportive of the study's overall aims and general design. This is because the study has already been through a scientific review (ethical approval as well as the Swedish Medical Agency and the trial will be registered at clinicaltrials.gov). The DSMB will

consider study-specific data as well as current relevant background knowledge about the disease, test agent, or patient population under study.

4.1 Objectives

The primary objective of the DSMB is to monitor the safety of the interventions and the validity and integrity of the data from the clinical study. Additionally, the DSMB will make recommendations to the sponsor regarding the continuation (if a too slow pace of recritument is noticed that could affect the safety of the study), modification, or termination of any or all arms of the study.

4.2 General Responsibilities

The general responsibilities of the DSMB are:

- To evaluate, on an ongoing basis, the accumulating safety assessments to ensure the ongoing safety of study subjects, more specific serious adverse events (SAEs). Study sites will report the following SAEs to the DSMB within 24 hours from getting to know an SAE event occurred and DSMB will report to the Swedish Medical Agency within 7 days for life-threating events and within 15 days for others. This is in order to keep the sponsor blinded for the results.

For the child:

- Intrauterine death or neonatal death up to 27 days after delivery
- Admission to neonatal intensive care unit for more than 48 hours before discharge home
- Umbilical cord prolapse

For the woman:

- Maternal death up to 42 days after delivery
- Mother admitted to intensive care unit
- Uterine rupture / hysterectomy in connection to the delivery

- Delivery outside the hospital or within 15 minutes from admission
- Woman re-admitted to the hospital due to serious events such as pulmonary embolism and sepsis after delivery within 42 days

The study coordinator at each study site will check the "Nationell Patient översikt" (NPÖ) once a month for unexpected serious re-admission postpartum. ICD-codes should be sent to DSMB for further decision if more information is warranted.

- Suspected unexpected serious adverse reactions (SUSARs) are reactions/events that are unexpected, serious, and suspected to be caused by the treatment, i.e. adverse events that are not included in the summary of product characteristics. Since this study is an investigator-initiated non-commercial study where the principal investigator lacks the ability to report directly into the European database of side effects (EudraVigilance),we therefore ask the Competent Authority for help. SUSAR is reported via CIOMS-form that will be sent to registrator@mpa.se.
- To consider and assess SAEs causal nature and time from the intervention to the SAE. To consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.
- It is of importance to notice that since this is a non-inferiority study; the study should not be stopped due to a positive difference in the primary composite endpoint and neither for futility (conditional power). The main aim is to check safety for the women and the fetuses and children involved in the study. An for the DSMB unblinded interim analyses should be made after 1000, 3500 as well as after 6000 randomized patients. The interim analyses should however be strictly blinded for the sponsor. **If safety is affected in one trial arm or patient group in such way that the trial arm or patient group is considered to be stopped/excluded from the study,**

the other trial arm or patient group should be considered to be continued. "Trial arm" refers to induction with either balloon catheter or oral prostaglandin. Patient groups that will be studied in subanalysis during the interim analyses are primiparous vs multiparous women and women induced due to prelabour rupture of the membranes (PROM) vs other reasons for induction.

- If the interim analyses shows serious complications in the outpatient group termination of the study or termination of one arm in the study should be considered and then suggested to the sponsor, who then will be able to take part in the analysis.
- The sponsor is the one deciding to stop the study or not. Data will be provided to the DSMB via the Swedish Pregnancy Register.
- Protect the confidentiality of the study data and the DSMB discussions.

5 DSMB CHAIR RESPONSIBILITIES

The following responsibilities are those of the DSMB Chair:

- Serves as a voting member
- Convenes the DSMB at interrims analyses as well as if necessary if an extraordinary SAE has happened
- Facilitates the meetings, assists in the development of the agenda, and ensures that the meeting minutes and recommendation(s) are appropriately documented
- Serves as the primary contact person for the DSMB
- Reviews and approves the Charter
- Ensures that those involved in the day-to-day management of the study are excluded from DSMB voting procedures

- Discusses DSMB recommendations with the sponsor and appropriate members of the project team via teleconference. This responsibility may be delegated to the Co-chair.
- Monitors that minutes from closed sessions of DSMB teleconferences is taken and preserved. Minutes will be taken by the DSMB co-chair.

6 THE RESPONSIBILITIES OF THE SPONSOR (STUDY COORDINATOR) AND THE STATISTICIAN - DELIVERING DATA TO DSMB

The following activities are the responsibility of the sponsor (study coordinator):

- Provides DSMB regularly scheduled reports 2 weeks prior to interim analyses. This is done blinded by using the Pregnancy Register and SCB for data concering SAEs from the different study sites
- Provides ad hoc reports requested by the DSMB in a timely and blinded manner
- Provides statistician to be available in the event that unmasking is requested

7 SPONSOR RESPONSIBILITIES

The following activities are the responsibility of the sponsor or, as clarified herein, its designee(s):

- Appoints the DSMB Chair and members
- Reviews and approves DSMB Charter
- Reviews and implements the DSMB recommendation(s), as appropriate
- Advises appropriate individuals of DSMB recommendations, and notifies regulatory authorities, other agencies, and investigators when required or necessary
- Reviews conflict of interest information and has authority for actions taken based on findings of conflicts
- Posts appropriate review materials for DSMB members

8 MEETINGS OF THE DSMB

8.1 Organizational Meeting

The first meeting of the DSMB will be an organizational meeting. This meeting will formally establish the DSMB and begin to acquaint the DSMB members with the protocol or types of protocols that this DSMB will be charged with monitoring. It affords the DSMB an opportunity to recommend final revisions to the Charter and the communication plan between the DSMB and the sponsor.

The attendees for this organizational meeting will include DSMB members and representatives from the sponsor.

At the beginning of the DSMB meeting, the Chair will initiate the organizational session of the meeting, which will include calling the meeting to order and assuring a duly constituted Board.

Meeting objectives will include:

- the introduction of the DSMB
- review of the DSMB Charter
- defining the roles and responsibilities of the DSMB
- developing procedures for conducting business (e.g., voting rules and quorum, attendance, etc.)
- brief discussion of the upcoming protocol(s) and the development of possible standard study status tables and listing shells

8.2 Scheduled Protocol and Data Review Meetings

Each protocol and data review meeting will consist of three sessions: Open Session, Closed Session, and Closed Executive Session.

8.2.1 Open Session

This will begin with an introductory session that includes introductions, roll call, assurance of a quorum, a reminder about the confidential nature of the proceedings and corresponding documentation, and a review of conflict of interest for all DSMB members.

Following the introductory session, the DSMB will move into the open session. Attendees will include the DSMB members, voting and *ex officio* members, the investigator and other study staff personnel, and sponsor members. This session may also be open to Center PIs, representatives for industrial collaborators, and representatives from the Swedish Medical Agency.

The open session will serve as a general study update. The PI will be called upon to present study status and known relevant findings. Others with specific safety experience or concerns may also be called upon to present. The session will provide a forum for an exchange of information among the various groups involved in the conduct of the study. It will afford the DSMB members an opportunity to question the project team about the study and to seek additional information deemed relevant to the data review. Discussions may include progress of the study, including adverse events, disease status of participants, comparability of groups with respect to baseline factors, protocol compliance, site performance, quality control, and timeliness and completeness of follow-up. Only masked data will be reviewed and/or discussed during the open session – as fare as possible during to the nature of the trial, e.g. delivery before reaching the hospital is an outcome only possible to occure in the outpatient group.

8.2.2 Closed Session

Following the open session of the meeting, a closed session involving the DSMB members will be held to review grouped safety data, discuss findings, develop recommendations, and obtain agreement on voting. During this session, any issues related to subject safety will be discussed. Requests by DSMB Members for the unmasking of data may be made at this time. Interim efficacy analysis planned a priori will be addressed in closed session.

8.2.3 Closed Executive Session

A brief teleconference will be held between the DSMB Chair and the specified sponsor representatives and possibly representatives for the Monitor to discuss the recommendations of the DSMB.

A brief summary that describes the individual findings, overall safety assessment, and DSMB recommendations will be agreed upon by the Chair and forwarded to the sponsor within one week of the meeting.

8.3 Unscheduled Meetings/Reports

Unscheduled meetings can be requested by any party with the responsibility of overseeing the study. Requests can be made to the DSMB Chair or the sponsor. The Chair, in collaboration with the sponsor, will schedule any unplanned meetings.

The DSMB may request special reports on an as needed basis. These requests will be made to the sponsor, who will direct the study statistician as appropriate.

9 COMMUNICATION

This DSMB can meet via teleconference call. An agenda will be provided detailing the protocol(s) to be discussed.

9.1 Reports to the DSMB

- Associated AEs of special interest will be provided to the DSMB at the interims-analyses or as requested by the Board.
- Study status reports will be provided to the DSMB at least one week prior to each scheduled meeting.

9.2 DSMB Minutes

The DSMB meetings may be audio taped for the purpose of documenting meeting minutes. Once the Chair approves the minutes, the tapes will be destroyed.

The sponsor will prepare the draft meeting minutes of the open session and forward to the DSMB Chair and the sponsor for review within one (1) week following the DSMB meeting. Minutes of the open session will describe the proceedings. Draft minutes will be distributed to chair of DSMB for review and comment.

Minutes of the closed session will describe the proceedings of the closed session. Minutes will be taken by the DSMB co-chair. If unmasked information is reviewed during the closed session, minutes containing unmasked information will be marked as "Confidential" and distributed to the members of the DSMB only.

At the conclusion of the study, a complete set of the minutes of the closed sessions and the closed reports will be sent to the sponsor.

9.3 Recommendations

Following the closed session, a brief teleconference will be held between the DSMB Chair and the specified sponsor representatives and possibly a Monitor representative to discuss the recommendations of the DSMB.

A brief summary that describes the individual findings, overall safety assessment, and DSMB recommendations will be agreed upon the Chair and forwarded to the sponsor within one week of the meeting.

The DSMB can recommend to the sponsor that the current study continues without modification, continues with specified modifications, discontinues one or more arms of the study (referring to mode of induction by either balloon catheter or oral prostaglandin), or halt or modify the study until more information is available (referring to exclude certain groups from participation, e.g. primiparous vs parous women, women induced for PROM vs other indications).

10 REVISIONS TO THE CHARTER

A draft of the Charter will be provided to the DSMB prior to the organizational meeting. During the organizational meeting, the Charter will be reviewed and revised as needed. The Chair and

the sponsor will approve all changes to the Charter. The version date will be displayed as a footer on all pages.

As needed, the Charter may be revised after the organizational meeting, with the Chair and the sponsor providing sign-off. Changes to the Charter will be clearly delineated in a document, and this document will be associated with the new version. A "track changes" version of the revised document should be created; this version would reveal all strikethrough and updated text.

11 COMPLETION OF DSMB ACTIVITIES

The DSMB will remain active until written notification is received from the sponsor.

12 DOCUMENT RETENTION

The DSMB members will maintain a copy of any relevant correspondence, meeting packets, DSMB reports, and meeting minutes in a secure area prior to the meeting occurrence.

Appendix A: DSMB Member Signature Page

Member Information

Role: DSMB Chair _____ Member ____

Voting Rights: Yes ____ No ___

Name:

Member Information

Affiliation:

Phone: Fax:

E-mail address:

Re: DSMB Charter Version Date: _____

I have reviewed the attached DSMB Charter and approve it as written. I understand my role as a member of this DSMB.

Signature: _____ Date: _____

Confidentiality and Non-Disclosure of Materials and Proceedings

Materials and information made available to the DSMB that are not in the public domain, as well as the discussions that take place during the meetings, are strictly confidential and must not be disclosed to or discussed with anyone who is not a member of the DSMB. Furthermore, confidential information obtained as a DSMB member may not be used by the member for personal benefit or for the benefit of the member's family, associates, or of organizations with which the individual is associated or has a financial involvement.

DSMB Certification Regarding Conflict of Interest, Confidentiality, and Non-Disclosure

NAME: _____

Primary employer: _____

[ ] I have read the attached NIEHS DSMB Conflict of Interest and Confidentiality Form and hereby certify that I do not have a conflict of interest or have discussed and resolved with the NIEHS ethics official any potential conflict of interest with the study(ies) reviewed by this DSMB.

[ ] I fully understand the confidential nature of the DSMB process and agree not to disclose or discuss the materials associated with the review or substance of any confidential discussions about the studies with any individual not a member of the DSMB or NIEHS staff or to use the information for my personal benefit or the benefit of others.

Signature: _____

Date: _____

To be completed annually.