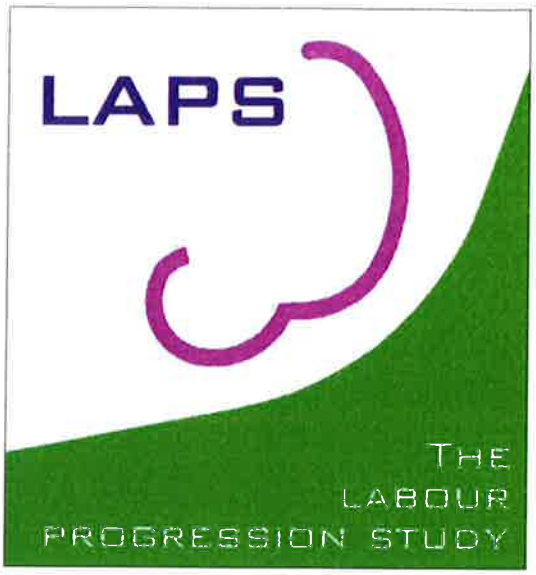

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PROTOCOL VERSION NO. 1- 21-05-2014

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SIGNATUR PAGE

I hereby declare that I will conduct the study in compliance with the protocol and the applicable regulatory requirements:

Pål Øian, Professor

P. Øian — Tromsø, May 27, 2014

Signature — *Place, date*

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Ellen Blix, Professor

Ellen Blix — Tromsø, May 23rd, 2014

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Stine Bernitz, Research Midwife/associate professor

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Torbjørn Moe Eggebø — Trondheim May 22nd 2014

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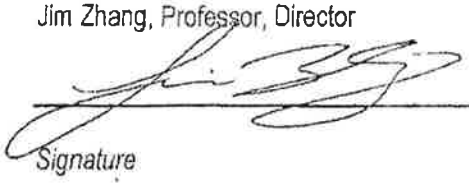
Jim Zhang, Professor, Director



Shanghai 5-23-2014

Signature *Place, date*

I hereby declare that I will conduct the study in compliance with the protocol and the applicable regulatory requirements:

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Fredrikstad 5-26-2014

Signature

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LeivSandvik, Professor

Leiv Sandvik Oslo, 5-26-2014

Signature *Place, date*

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EXPLANATION OF TERMS

Clusters – Birth care units in Norway

Progression curve – A curve showing the expected labour progression throughout labour

Labour dystocia – A definition of when the labour progression is slower than what is expected to be normal

Labour stages:

Latent first stage – painful contractions and some cervical change including cervical effacement and dilatation up to 4 cm

Established first stage – regular painful contractions and progressive cervical dilatation ≥ 4 cm

Passive second stage – full dilatation of the cervix prior to or in the absence of involuntary compulsive contractions.

Active second stage – Time from start of active pushing to delivery (1)

Local coordinator – Midwife responsible for the trial at each birth care unit

Robson group I – Nulliparous women with a singleton vertex fetus and spontaneous onset of labour, gestational age ≥37 weeks

1 INTRODUCTION

1.1 Background

There is no worldwide consensus on duration of labour after spontaneous onset of labour, and therefore, there is no consensus on the definition of prolonged labour (labour dystocia). The progression of labour is traditionally measured by the dilatation of the cervix over time, but the expected progression per time unit varies between and within countries. The duration of labour and labour curve patterns are still subjects to discussion (2).

In 1954, Emanuel Friedman presented the first progression curve based on labour course data on 100 nulliparous women (Figure I) (3). Friedman's curve has been widely adopted and applied in clinical practice internationally for almost 60 years. In 2002, Jim Zhang presented an alternative labour curve based on 1329 low-risk women with spontaneous onset of labour (Figure II) (4). Zhang's replicated these findings in a large cohort of 26,838 women in 2010 (5).

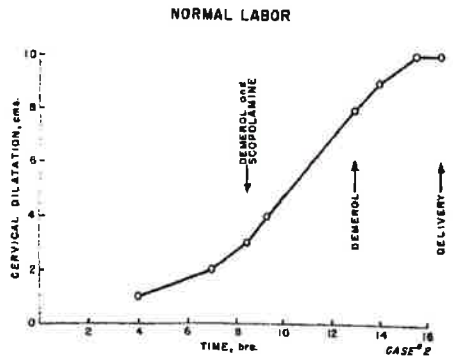

Figure I. Emanuel Friedman's curve of cervical dilatation in nulliparous women (1954)

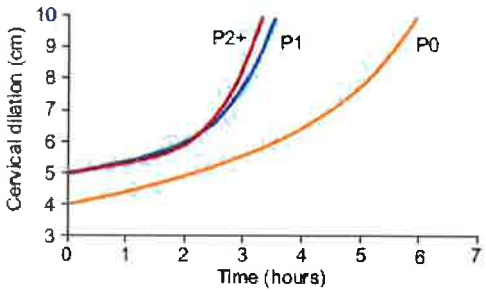

Figure II. Jim Zhang's curve of cervical dilatation (2010)

Zhang's curve differs distinctly from the Friedman's curve in that the cervix dilate substantially slower, especially before reaching six centimetres of dilatation, nor is the deceleration phase in Friedman's curve found in Zhang's curve. These findings may suggest that the diagnostic criteria for labour dystocia following Friedman's curve are too stringent in contemporary birth care.

Labour dystocia is characterised by abnormally slow progression of the labour process and is among the most common challenges of birth care especially in nulliparous women (6,7), as labour dystocia is the most common reason for emergency caesarean sections (8).

Labour dystocia is most often initially treated with amniotomy, followed by oxytocin infusion to augment the contractions of the uterus. Oxytocin is a potent drug and is classified by the Institute for Safe Medication Practices, US, as one out of 12 medications, which is "bearing heightened risk of harm" (9). Even when used correctly, oxytocin is found associated with increased risk of instrumental vaginal delivery, episiotomy (10), emergency caesarean section, sphincter ruptures, low Apgar score, low pH in neonates, and transfer of the new-born to a neonatal intensive care unit (11). If augmentation with oxytocin does not lead to an adequate effect on labour progression, a caesarean section is performed. An uncomplicated vaginal birth in nulliparous women strongly predicts uncomplicated labour and delivery in subsequent pregnancies (12), while emergency caesarean sections are associated with lower rates of breastfeeding, and increased risk of post partum depression (13), anaemia, hysterectomy (14), stillbirth and uterine rupture in subsequent pregnancies and deliveries (15). Neonates delivered by caesarean section have an increased risk of respiratory distress post partum (16) and infant asthma and allergies (17).

1.2 Rationale for the trial

Nulliparous women with a singleton vertex infant and spontaneous onset of labour at term are usually considered at low-risk of adverse birth related outcomes, and, thus, they have a considerable potential of spontaneous course of labour without interventions. Even so, the rate of augmentation with oxytocin in low-risk nulliparous women is high in Scandinavia. Over the last decade the rate in Norway has been reported in research articles to be from 44 to 62 % (10,18,19). High rates of oxytocin augmentation have not been found to reduce caesarean section rates or to improve birth related outcomes for mother or baby. (6) The rates of emergency caesarean sections in low-risk nulliparous women with spontaneous onset of labour were about 9 % in Norway (20) in 2012.

A graphic record of labour progression, often called a partogram, is widely used. A partogram enables midwives and doctors to monitor labour progression during the course of labour, and, according to a certain set of criteria for labour dystocia, to carry out necessary interventions. In Norway the expected progression of labour is close to linear and based on interpretations of Friedman's curve (Figure I) (3). The definition of labour dystocia varies from institution to institution; although a definition in accordance with WHO recommendations is widely used and recommended by the Norwegian Society in Obstetrics and Gynecology (when cervical dilatation crosses the 'action line' 4 hours from the 'alert line'). The evidence of the definition is vague, and contemporary research has shown that normal labour can last substantially longer, especially at an early stage of labour without jeopardising outcomes for the mother or neonate (8,21).
A new dynamic guideline for labour progression is developed according to contemporary research findings by Zhang et al. (21). This guideline differs from guidelines based on an interpretation of Friedman's research by not expecting a linear progression and by defining the progression to be normal if the rate of cervical dilatation is within the 95 percentile of the duration in Zhang's material of spontaneous labours (Appendix A).

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

The main aim of this trial is to evaluate in what way two different guidelines for diagnosing labour dystocia, one based on and interpretation of Friedman's research, and one based on Zhang's research of labour progression, affect maternal and neonatal outcomes related to delivery among nulliparous women with a singleton vertex infant and spontaneous onset of labour, gestational age ≥37weeks. Overall we wish to monitor and document procedures and outcomes in relation to the labour process.

2.1 Primary Endpoint

- The rate of emergency caesarean sections

2.2 Secondary Endpoints

- The rate of oxytocin augmentation during labour
- The rate of instrumental vaginal deliveries
- The rate of artificial rupture of membranes (amniotomy)
- The rate of electronic fetal monitoring (CTG or CTG+STAN)
- The rate of epidural analgesia
- The rate of episiotomies
- The rate of perineal tears grade 3 and 4
- The rate of dystocia
- Postpartum haemorrhage
- Blood transfusion
- Apgar scores
- Ph in the umbilical artery
- The rate of transfers of neonates to the Neonatal Intensive Care Unit (NICU)
- Mean score of women's experience with child birth (measured by :"The Childbirth Experience Questionnaire, CEQ" (22), (Appendix B)
- Mean duration of labour (active phase of first stage, latent phase of second stage, expulsion phase and second stage in total)
- Detailed measures of oxytocin augmentation (mean length of augmentation, dosage, and administration throughout labour)

We will also register the following variables:

Indications for interventions, cervical dilatation at onset of oxytocin augmentation and amniotomy, reason for admittance and length of stay in NICU and compliance with the protocol.

3 STUDY POPULATION

3.1 Selection of Study Population

The projected clusters (birth care units) are:

- Østfold Hospital Trust, University Hospital in Northern Norway, Innlandet Hospital Trust: Lillehammer, Innlandet Hospital Trust: Elverum, Vestfold Hospital Trust, Vestre Viken Hospital Trust: Bærum, Vestre Viken Hospital Trust: Drammen, Stavanger University Hospital, Møre and Romsdal Hospital Trust: Ålesund, Møre and Romsdal Hospital Trust: Molde, Nordland Hospital: Bodø, Sørlandet Hospital: Arendal, St. Olavs Hospital and Telemark Hospital.

3.2 Number of Participants

We expect to collect data on 6582 deliveries from the cluster birth care units for analysis on an individual level. This corresponds to approximately 470 per cluster. The design allows for flexibility, so that larger birth care units may contribute with more study subjects than smaller units.

3.3 Inclusion Criteria

Norwegian birth care units (>500 deliveries per year) that are willing to adhere to the allocated guideline for all Robson group I women during the study period, and who consider that they have the capacity to participate both logistically and in practice.

4 OVERALL STUDY DESIGN

4.1 Hypothesis

We hypothesise that adhering to the guideline for labour progression presented by Jim Zhang (21) (figure II) will decrease the rate of emergency caesarean sections and augmentation with oxytocin among low-risk nulliparous compared to adhering to guidelines for labour progression based on a modified Friedman's curve (3) (figure I), without jeopardising the outcome for mother or neonate.

In this multicenter trial we include 14 birth care units Norway. Each cluster will be randomly allocated to either intervention or control arm.

Intervention - Labour progression guideline in the intervention clusters (Zhang's guideline, Z):
During established first stage of labour, i.e. regular painful contractions and cervical dilatation ≥ 4 cm (1), dystocia is diagnosed if the cervix dilatation rate does not meet the expected progression according to Zhang's findings (Appendix A). During second stage of labour, dystocia is diagnosed, if the time from full dilatation to active expulsion phase (passive second stage) exceeds 1 hour and 45 minutes (2 hours and 30 minutes for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes. This progression curve is based on contemporary research on labour progression by Jim Zhang (Appendix A).

Control - Labour progression guideline in the control clusters(based on Friedman's guideline, F): During established first stage of labour, i.e. regular painful contractions and cervical dilatation from 4 cm (1), dystocia is diagnosed if cervix dilatation rate is less than 1 centimetre per hour assessed after 4 hours (crossing the 4-hours action line). During second stage of labour, dystocia is diagnosed if the time from full dilatation to active expulsion phase (passive second stage) exceeds exceeds 1 hour (2 hours for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes.

The randomisation process will be performed through a central computer assisted programme which stratifies by number of deliveries and the rate of caesarean sections for Robson group I at each unit per year. The trial will be conducted according to the CONSORT statement for planning and implementation of cluster randomised trials (23).

We believe that cluster randomisation, i.e. randomisation at hospital level, is superior to individual randomisation as choosing individual randomisation for this specific study would imply substantial risk of contamination.

Estimated activities in the trial period:

	2014/2015				2015/2016				2016/2017			
Activity	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Inclusion and randomisation of clusters												
Guideline instructions at clusters												
Enrolment of participants												
Patient satisfaction questionaire												
Control of data												
Data analyses												
Production and publication of articles												
Final report to policy makers												

4.2 Test of the applicability of Zhang's guideline

We will test the applicability of Zhang's guideline for labour progression with respect to the understanding and the use of the guideline during labour. A small number of midwives will be asked to participate in testing the guideline. They will receive Zhang's guideline for labour progression along with written instructions about how to use the guideline, and a number of constructed labour cases on which they can test the applicability of the guideline. Afterwards the midwives are invited to participate in a workshop with the PI. In the workshop the midwives will be encouraged to share experiences from their work with the guideline and go through each case example and the guideline together with the PI. Experiences and comments from the midwives will then be used to adjust guideline, written instructions, and the protocol, if needed.

5 STUDY PROCEDURES

5.1 Flow Chart

See appendix C for flow chart of cluster inclusion and expected number of individuals for analysis.

5.2 Invitation to Clusters

All eligible clusters in Norway will receive a concise edition of the protocol and a written invitation to participate in the trial.

5.2.1 Cooperation agreement

A cooperation agreement must be signed by each cluster at inclusion. Each cluster must provide one local coordinator, who will be responsible for the trial during the study period (see point 5.4).

5.2.2 Baseline data

The following baseline data will be collected for each cluster:

- Number of Robson Group 1-deliveries in 2012
- The rate of emergency caesarean sections in Robson Group 1 in 2012

5.3 Individuals

All Robson group I women giving birth at the included birth care units during the study period will adhere to the allocated guidelines for labour progression, which the birth care unit is randomised to.

5.3.1 Informed consent

All nulliparous women planning to give birth at any of the included birth care units will receive written information about the trial from the midwife in antenatal care, when called for routine ultrasound, at the ultrasound control or at the labour ward. Eligible women will be asked to sign an informed consent permitting her data to be included in the analyses and to answer a questionnaire on childbirth experience, four weeks after birth. All nulliparous women will have a trial sticker put on the antenatal record to make identification easier on admission for assessing Robson group affiliation.

5.3.2 Baseline data

- Age
- Height
- Prepregnant weight
- Civil status
- Education
- Smoking
- Gestational age at onset of spontaneous labour

5.4 Guideline instruction and local coordinators

The PI will introduce the allocated guideline to each cluster. At each cluster, one person responsible for the trial at the specific birth care unit (local coordinator) will be designated. The local coordinator is responsible for inclusion of participants, record control of each participant and for the local implementation of the trial. The local coordinators will act as contact persons to PI, and they must report any challenges to her.

5.5 Procedures for Discontinuation

5.5.1 Cluster Discontinuation

The reason for discontinuation of included clusters will be recorded. Clusters who withdraw from the trial after randomisation will be sought replaced by an equivalent cluster.

5.5.2 Trial Discontinuation

The trial may be discontinued at the discretion of the trial manager in the event of any of the following:

- Occurrence of adverse events unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of clusters or individuals

The trial manager and PI will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action.

6 ASSESSMENTS

6.1 Consecutively Assessments

Consecutively assessments e.g. vaginal explorations, fetal monitoring and interventions will be conducted throughout labour.

6.2 Safety Assessments

All Robson group I women in both arms will be cared for and monitored according to the procedures at each birth care unit. Necessary interventions due to the mother's or the fetus' needs, will be conducted regardless of the allocated guidelines for labour progression.

7 DATA MANAGEMENT AND MONITORING

7.1 Data collection during delivery

At each labour ward the midwife on duty will identify Robson group I women and make sure that the allocated guideline is followed. During labour the midwife responsible for the labour care, keeps record as usual in the electronic medical record and on paper when it comes to Zhang's guideline. For all women with a signed consent who have allowed their data to be included in the trial, the local coordinator will fill in the web-CRF.

7.2 Web-Case Report Forms (Web-CRFs)

Due to different systems for electronic medical records, and due to additional handwritten records, a web-based case report form (web-CRF) is being designed by the Unit of Applied Clinical Research at the Faculty of Medicine at the Norwegian University of Science and Technology, (NTNU). The web-CRFs will be a web-based programme accessible to the local coordinators which will enter all variables. Each participant will be registered by their inclusion number. The system will generate the inclusion number depending on which local coordinator that is logging in, to ensure that the inclusion number is unique. The inclusion numbers will indicate unit and local inclusion number. The web-CRFs are transferable to statistical programmes, such as STATA and SPSS. All clusters will get access to the web-CRF with boxes for all required information.

The local coordinators will ensure that the data required from the protocol is entered into the web-CRF, that the data are complete and accurate, and that entry is performed in a timely manner. She will also ensure that each woman is eligible for the trial before entering her data in the web-CRF. The signature of the local coordinators will attest the accuracy of the data on each web-CRF. If any assessments are omitted, the reason for such omissions will be registered in the web-CRF. Also subsequent corrections in the reporting in web-CRF, including the reason for the corrections, will be recorded. (See appendix E for information on the web-CRF from NTNU).

7.3 Questionnaire regarding the childbirth experience

Four weeks after birth all Robson group I women at the included birth care units will receive a request to complete an online questionnaire regarding birth experience, the Childbirth Experience Questionnaire CEQ. (Appendix B).

7.4 Confidentiality

The Trial Manager shall arrange for the secure retention of the participant identification and the code list. Participant files shall be kept for the maximum period of time permitted by each birth care unit. The trial documentation shall be retained and stored during the trial and for 10 years after trial closure. All information concerning the trial will be stored in a safe place inaccessible to unauthorized personnel.

8 STATISTICAL METHODS AND DATA ANALYSIS

8.1 Determination of Sample Size

The determination of the sample size (number of clusters and individuals for analysis) is based on a power calculation with the least occurring primary outcome; emergency caesarean section, which is 9.2 % in the study population (p1). Further, we expect that the emergency caesarean section rate will be 6.9 % (p2) when using the new guideline for labour progression.

Formula (4) on page 320 in the article by Hayes et al. (24) is used to calculate the needed number of clusters and participants. According to this formula, with a chosen significance level of 0.05, a power of 80 % and p1=9.2 % and p2=6.9 %, we will have to include at least 14 clusters using the allocated guideline in 6582 Robson group I women.

All statistical analysis will be conducted in STATA, SPSS or similar statistical software.

In the 14 clusters there will be approximately 8000 women fulfilling the inclusion criteria per year (2012). With an expected inclusion of 90 % and a dropout of 10%, the required numbers of women should be included within 10-12 months.

8.2 Randomisation

8.2.1 Allocation-sequence generation

Key elements to specify regarding allocation of treatment are:

- The method of generating the allocation sequence is computer-generated
- The allocation ratio is equal to one
- The type of randomisation is restricted
- The factor; size of birth care unit and rate of emergency caesarean sections will be used for stratification

8.3 Planned analyses

The main statistical analysis is planned when all data is collected and the files are merged.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of data base lock. The statistician will perform analysis blinded to the participant's affiliation to the groups as a control of the analysis.

8.4 Statistical Analysis

The analyses will be conducted according to the principle of intention-to-treat to estimate the effect of assigned guideline. The difference between groups will be presented with a risk ratio (RR) and a 95 % confidence interval (95% CI). For dichotomous efficacy variables a significance test taking into account the cluster structure of the data will be used (25). In the case of a substantial lack of adherence due to missing data, also 'as treated' or 'per protocol' analyses will be performed to estimate the effect of used guideline, after appropriate adjustment via inverse probability weighting or g-estimation (26,27).

9 STUDY MANAGEMENT

9.1 Investigator Delegation Procedure

The trial manager is responsible for making and updating a "delegation of tasks" with the listing of all the involved co-workers and their role in the project. The PI will ensure appropriate introduction and continuous updating, if relevant, of the study at each cluster.

9.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
If any, significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

9.3 Study Amendments

If the study protocol is revised, the amendment and/or a new version of the protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the ethics committees according to EU and national regulations.

9.4 Audit and Inspections

Authorized representatives of a competent authority and ethics committee may visit the centres to perform inspections, including source data verification. The purpose of an inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol and any applicable regulatory requirements. The PI will ensure that the inspectors and auditors will be provided with access to source data/documents.

10 ETHICAL AND REGULATORY REQUIREMENTS

The trial will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and applicable regulatory requirements. Registration of individual data will be carried out in accordance with national personal data laws.

All women will be cared for in accordance with each birth care unit's normal procedures with respect to criteria for admission, attendance of a midwife, pain relief, mobilisation and nutrition.

10.1 Ethics Committee Approval

The protocol was approved by the Regional Committees for Medical Health Research Ethics in Norway (2013/1862/REK sør-øst).

The PI is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

10.2 Other Regulatory Approvals

The management at each birth care unit must agree to follow the protocol before commencement of the trial.

The protocol will be registered in www.clinicaltrials.gov before commencement of the study.

10.3 Informed Consent Procedure

Participants will be informed, that their medical records will be reviewed for trial purposes by authorized personnel, following strict regulations for confidentiality.

It will be emphasized that the participation is voluntary, and choosing not to participate will not prejudice her subsequent care. Documented informed consent must be obtained for all participants before including any data in the analyses. This will be done in accordance with the national and local regulatory requirements. The local coordinators are responsible for obtaining signed informed consents.

A copy of the participant information and consent will be given to the participants. The signed and dated consent forms will be filed in the Investigator Site File binder and also scanned to be part of the patient's electronic medical record at the hospitals.

10.4 Subject Identification

The local coordinators are responsible for keeping a list of all included participants including date of birth and personal number, full names and last known addresses.

The participants will be identified in the web-CRF by inclusion numbers.

11 TRIAL SPONSORSHIP AND FINANCING

Financing of a one year postdoctoral position is granted from the Østfold Hospital trust. Additional financing for a two years postdoctoral position (2015 – 2016) and a three year PhD position will be applied for at the South-Eastern Norway Regional Health Authority.

12 TRIAL INSURANCE

Participants are covered by the Norwegian Patient Compensation System.

13 PUBLICATION POLICY

All colleagues, who have contributed significantly with the planning and/or performance of the study (Vancouver convention 1988), may be included in the list of authors.

Preliminary planned publications:

- *Paper 1:* The Labour Progression study, evaluating the use of a new partogram in labour care for low-risk nulliparous women. A protocol of a cluster randomised trial in Norway
- *Paper 2:* Is it possible to reduce the rate of emergency cesarean section in low-risk nulliparous without compromising maternal and fetal health? – A cluster randomised trial
- *Paper 3:* Is it possible to reduce the rate of augmentation in low-risk nulliparous without compromising maternal and fetal health? - A cluster randomised trial
- *Paper 4:* How does the amount of oxytocin during labour affect the outcome in neonates? - A cohort of low-risk nulliparous women
- *Paper 5:* The use of oxytocin and labour progression in obese women.– A cohort of low-risk nulliparous women
- *Paper 6:* Does the expected labour progression according to contemporary research, correlate with labour progression in low-risk nulliparous women? - A cohort of low-risk nulliparous women
- *Paper 7:* Low-risk nulliparous women's childbirth experience labour according to two guidelines for expected progression of labour - A cluster randomised trial

Ownership and use of data:

The ownership of the data generated at each unit belongs to each of the included hospitals. The project group has managerial prerogative over the data entered into the web based case report form, designed for this study. The managerial prerogative is not in hindrance with each hospital's right to publish their own data after

publication of planned articles, provided that it is not in conflict with planned publications. Provided that the criteria for authorship is fulfilled, according to the International Committee of Medical Journal Editors (ICMJE), one author from each hospital is invited to participate as co author of one of the planned publications.

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15 LIST OF APPENDICES

15.1 Appendix A - **Zhang's curve for progression of labour included instructions**

15.2 Appendix B– **Questionnaire for childbirth experience, No**

15.3 Appendix C – **Flow chart of inclusion**

15.4 Appendix D – **Request for participation in a research project**

15.5 Appendix E – **Information on web-CRF, NTNU**

Additional information to the Protocol.

Additional information to Figure 1, page 7:

The medications Demerol and Scopolamin are administrated at time point in labour indicated by the arrows in the curve.

Demerol is a synthetic opioid. Scopolamin is a hyoscine, often used against nausea.