STATISTICAL ANALYSIS PLAN	
Study Title:	Dilapan vs Misoprostol for cervical ripening [COMRED – comparison of Misoprostol ripening efficacy with Dilapan]
Study Ref.:	AAAR8566

DOCUMENT HISTORY		
VERSION NO.:	**DATE**	**PURPOSE OF REVIEW/UPDATE:**
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DOCUMENT APPROVAL INFORMATION			
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1. OVERVIEW AND STUDY PLAN

1.1. STUDY DESIGN

This is a non-inferiority, unblinded, randomized, controlled trial where 322 eligible participants undergoing IOL at ≥37 weeks gestation at CUMC and admitted to labor and delivery unit will be enrolled and randomly assigned in a ratio 1:1 to either receive Dilapan-S® or Misoprostol for cervical ripening.

2. STUDY PROCEDURES

After randomization all participants will undergo assessment as per the floor protocol including Bishop score. Patients will have either 1-5 Dilapan-S® rods inserted into their cervix by the providers or receive 25 mcg of misoprostol orally every 2 hours to a maximum of 6 doses over 12 hours. Patients will be examined after 12 hours, Dilapan-S® rods will be removed and Bishop score will be reassessed. Patients in both groups will be evaluated for artificial rupture of membranes and initiation of oxytocin for inducing uterine contraction. A diagnosis of failed IOL will be made if patient does not go into active labor within 24 hours after initiation of Oxytocin and AROM. Intrapartum management will be according to institutional guidelines. All study participants will be contacted by phone 2 weeks after enrollment to find out if they needed any additional treatment following discharge. All study patients will be asked to fill out a questionnaire regarding their experience with the method of induction. Data will be collected by chart review and analysed based on the outlined statistical plan.

3. OBJECTIVES

The objective of this study is to assess the efficacy of Dilapan-S® for cervical ripening compared to Misoprostol in women undergoing IOL at or more than 37 weeks gestation.

3.1. PRIMARY OUTCOME

Proportion of women achieving vaginal delivery within 36 hours of intervention.

3.2. SECONDARY OUTCOMES

Individual and composite maternal and fetal outcomes including overall vaginal delivery rate, cesarean section rate, Bishop score after cervical ripening, infections, postpartum hemorrhage. Neonatal outcomes include Apgar scores, NICU admission and sepsis.

Secondary endpoints are:

- Overall vaginal delivery rate in each group
- Rate of caesarean deliveries in each group
- Rate of operative deliveries (vaginal plus caesarean)
- Bishop score at 12 hours after the intervention and change in Bishop score
- Percentage of subjects who did not receive all 6 misoprostol doses
- Percentage of subjects with failed Dilapan-S insertion
- Percentage of subjects delivering vaginally in 24 hours after the initiation of intervention

- Delivery time
- Initiation of cervical ripening to delivery time
- Initiation of oxytocin to delivery time
- Total length of hospital stay
- Maternal outcomes:
  - Chorioamnionitis
  - Endometritis within 2 weeks after delivery
  - Postpartum haemorrhage (EBL>1000cc and/or drop in HCT by 10 points)
  - 3rd and 4th degree lacerations
- Neonatal outcomes:
  - Apgar score <7 at 5 min
  - Cord arterial blood pH and Cord arterial blood pH <7
  - Cord arterial blood base excess and Cord arterial blood base excess > -12mmol/l
  - NICU admission within 2 weeks after study intervention
  - Antibiotic use within 2 weeks after study intervention

3.3. SAFETY ENDPOINTS

3.3.1. UNDESIRABLE SIDE EFFECTS

- Fever, nausea, vomiting and diarrhoea
- Uterine tachysystole
- Hyperstimulation
- Uterine hypertonus
- Failed induction of labor, arrest of first and second stage of labor
- Abnormal fetal heart tracing during cervical ripening
- Intrapartum fever

3.3.2. COMPLICATIONS SPECIFIC TO DILATOR INSERTION

- Vaginal bleeding
- Rupture of membranes
- Cervical laceration
- Excessive pain causing need for analgesia during cervical ripening
- Vasovagal reaction during insertion of the device
- Entrapment of the device
- Fragmentation of device during removal or insertion
- Retraction of device into uterine cavity.
- Failure to insert Dilapan-S®

4. HYPOTHESIS

The hypothesis is based on the primary objective and one primary outcome, which is proportion of women achieving vaginal delivery within 36 hours of intervention.

Null hypothesis states that Dilapan-S is inferior to Misoprostol in efficacy for cervical ripening for induction of labor.

$$H_0: p_M - p_D \geq \delta$$

Alternative hypothesis states that Dilapan-S is non-inferior to Misoprostol in efficacy for cervical ripening for induction of labor.

$$H_A: p_M - p_D < \delta$$

4.1. INTERIM ANALYSIS

The data was reviewed by Data and Safety Monitoring Board (DSMB) to ensure the safety aspects of the study. Data was presented without revealing the randomization.

5. DETERMINATION OF SAMPLE SIZE

The study is powered at 85% for detecting the primary outcome with a type 1 error at 2.5% for one-sided test.

6. STATISTICAL PRINCIPLES

6.1. GENERAL STATISTICAL CONSIDERATIONS

The statistical analyses will be performed in accordance with ICH E9 guideline (ICH E9, 1998) and is based on all collected data. Statistical analyses will be performed at the 5% significance level.

The quantitative variables will be summarized using the following parameters:

- Number of non-missing data,
- Mean,
- Standard deviation,
- Median,
- Minimum and Maximum (range),
- First and Third quartiles (interquartile range).

The categorical/qualitative variables will be summarized using the following parameters:

- Number of non-missing data,
- Frequencies and percentages.

All collected data will be presented in data listings.

6.1.1. MEASURES TO ADJUST FOR MULTIPLICITY, CONFOUNDERS AND HETEROGENEITY

Only one primary objective, outcome and pair of hypotheses is set. Subgroup/Covariate analyses will be introduced as sensitivity analysis if appropriate.

6.1.2. DESIGN TECHNIQUES TO AVOID BIAS

This is a prospective, randomized, controlled, open-label clinical trial to assess the performance and safety.

6.1.3. MISSING VALUES, OUTLIERS AND OTHER DATA CONVENTIONS

The analysis will be conducted per protocol.

Besides, for primary and secondary objectives that explore trends over time, in the case of intermediate or final missing data, these will be replaced in accordance with the "intention to treat" method (ITT) and in particular by using the LOCF (last observation carried forward) method.

6.2. ANALYSIS POPULATIONS

6.2.1. SAFETY POPULATION

The Safety population will be comprised of all subjects in whom Dilapan-S® was inserted or who received at least one dose of misoprostol. This population will be based on the actual treatment received if this differs from that to which the subject was randomized. This population will be used for the analysis of safety data.

6.2.2. INTENT-TO-TREAT POPULATION (ITT)

ITT includes all patients that were randomized into the study. ITT subjects will be analysed in accordance with their randomized study treatment (i.e. in the treatment group they were originally allocated, regardless of treatment actually received). ITT will be used for evaluation of the baseline characteristics and as the primary population for efficacy assessments.

6.2.3. PER PROTOCOL POPULATION (PP)

PP is a subset of ITT patients who received study treatment. Following patients will be excluded from the PP population:

1. Patients with major protocol violation affecting the efficacy endpoints. Major protocol violations include (but are not limited to):
   a. Treatment assignment error
   b. Violation of one or more inclusion/exclusion criteria
   c. Use of forbidden medication
2. Patients who were prematurely withdrawn
3. Patients with missing data for the evaluation of the primary endpoint

This list can be extended based on a knowledge of other serious issues appearing in the data.

PP population will be used for evaluation of efficacy endpoints as a sensitivity analysis.

7. STATISTICAL METHODS

7.1. ANALYSIS OF BASELINE CHARACTERISTICS

Demographic data will be summarized.

7.2. ANALYSIS OF THE PRIMARY ENDPOINT

The primary outcome is the proportion of subjects achieving vaginal delivery within 36 hours after the initiation of the cervical ripening in Misoprostol and Dilapan-S® groups. Proportion of patients in each group and their difference will be calculated. One-sided 97.5% confidence interval[1] adjusted for the stratification factors (parity and gestational age) will be calculated for the difference in the proportions and conclusion about non-inferiority will be drawn from it taking into consideration a 10% non-inferiority margin. Unadjusted confidence interval will be calculated as well.

Additionally, the primary outcome will be analysed for each stratification factor. Mantel-Haenszel test will be used to test the difference between the subgroups.

7.3. ANALYSIS OF SECONDARY ENDPOINTS

All quantitative secondary variables will be summarized separately for each arm. Means of the two treatment arms will be compared with two-sample t-test and Wilcoxon rank-sum test as appropriate.

All secondary variables involving rates and percentages, will be calculated for both arms. Difference in proportions will be derived together with a 95% two-sided confidence interval. The difference between treatment groups will be concluded if the confidence interval does not include zero.

Maternal and neonatal outcomes will be summarized as reported in the CRF.

Delivery time will be presented using Kaplan-Meier curves with censoring for caesarean delivery.

7.4. SAFETY ANALYSIS

Exploratory variables will be evaluated from the adverse event and device deficiency reports. Number of cases and proportion of patients will be presented.

[1] Lower limit of two-sided 95% confidence interval is same as using one-sided 97.5% confidence interval.

SOFTWARE DOCUMENTATION

All summaries and statistical analyses, tables, figures and listings will be created with SAS® 9.4.

TABLES, GRAPHS AND LISTINGS

Baseline characteristics

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Table 14.1.2 Summary statistics of Demographic data

Table 14.1.3 Summary statistics of Baseline characteristics

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Listing 16.2.4.8 Neonatal Post-Partum data

ABBREVIATIONS

AROM	Artificial Rupture of Membranes
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CUMC	Columbia University Medical Center
DSMB	Data Safety Monitoring Board
EBL	Estimated Blood Loss
EMA	European Medicines Agency
HCT	Hematocrit
ICH	International Conference on Harmonization
IOL	Induction of Labour
ITT	Intent to Treat
NICU	Neonatal intensive care unit
PP	Per Protocol

REFERENCES

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ICH E3. (1996). *ICH Topic E3 Structure and Content of Clinical Study Reports.* The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

ICH E9. (1998). *Statistical Principles of Clinical Trials (E9).* The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

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