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Multicentre double-blind randomised placebo-controlled four-arm trial to assess the effect of oral sodium bicarbonate and intravenous hyoscine butylbromide on spontaneous delivery after induction of labour in nulliparous women: protocol for the Safe Induction of Labour Trial (SAINT)

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ABSTRACT

Introduction Presently, more than one in four births in high-income countries undergo labour induction. Induction of labour is an independent risk factor for adverse obstetric outcomes, including high rates of operative delivery. Two drugs, hyoscine butylbromide and sodium bicarbonate, have been used in labour to facilitate cervical dilation and prevent uterine lactate accumulation. However, no previous randomised trial has systematically studied the separate and combined effects of these drugs in women with induction of labour.

Methods and analysis The Safe Induction of Labour Trial (SAINT) study will assess the efficacy of oral sodium bicarbonate and intravenous hyoscine butylbromide on facilitating spontaneous (ie, non-operative) delivery in nulliparous participants with induction of labour. We present a 2×2 factorial design where three active treatment arms are compared with double-placebo. Participants are recruited at 10 delivery departments across Norway. Treatment will start on diagnosis of established labour with a maximum of three consecutive doses 4 hours apart. Approximately 5100 women will be screened to achieve 3000 participants randomly assigned to study intervention.

Statistical analyses The primary outcome of spontaneous delivery will be analysed using binary logistic regression. Results will be presented as marginal adjusted risk differences between each of the three active treatment groups and the double-placebo group.

Ethics and dissemination The SAINT study is approved by the Regional Committee for Medical and Health Research Ethics, the European Union Clinical Trials Information System, the Norwegian Medical Products Agency and Institutional Review Boards. Results will be disseminated in peer-reviewed journals and communications to congresses.

Trial registration number Clinical Trials: NCT05719467. EudraCT/EUCT: 2021-000392-37/2024-511848-55-00.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Safe Induction of Labour Trial study is a randomised controlled double-blind trial testing the effect of two common drugs on the rate of spontaneous (ie, non-operative) delivery in nulliparous women where labour is induced.
⇒ During active labour, repeat doses of the two drugs, intravenous hyoscine butylbromide and oral sodium bicarbonate, will be given in a 2×2 factorial design where three active treatment arms are compared with double-placebo.
⇒ This nationwide multicentre study is powered to detect a 15% difference in spontaneous delivery rates, which is deemed clinically significant.
⇒ We include patient-reported outcome measures to assess the participants' birth experience and postpartum consumption of health and social services.
⇒ The study includes nulliparous women at term with a singleton live cephalic fetus, thus results will not be extendable to multiparous women.

INTRODUCTION

Background and rationale

Over the last few decades, the rates of labour induction have increased steadily. Across high-income countries, more than one in four births is induced.[1 2] There is evidence that several groups of women benefit from labour induction, including those with pre-eclampsia,[3] post-term pregnancy,[4 5] pre-gestational diabetes,[6] a large-for-gestational-age fetus,[7] gestational diabetes,[8] preterm and pre-labour rupture of membranes,[9 10] twin pregnancy[11] and intrahepatic cholestasis of pregnancy.[12] At the same time, induction of labour is an independent risk factor for adverse obstetric outcomes, including caesarean section, instrumental delivery, postpartum haemorrhage, chorioamnionitis, labour dystocia, precipitate labour and neonatal acidosis.[13 14] A recent Norwegian nationwide clinical practice pilot study demonstrated that the rate of intervention was high as 44% of nulliparous women with labour induction experienced operative delivery.[15] Given that induction of labour is a common procedure that increases the risk of several major obstetric complications, interventions that may reduce the rate of operative delivery and facilitate safe delivery are highly warranted, particularly in nulliparous women.

Antispasmodics are commonly administered during labour in both developing and developed countries, but the rationale for such treatment is limited.[16] The uterine cervix is composed of connective tissue, but with a smooth muscle sphincter near the internal os, innervated by parasympathetic nerve fibres.[17] Hence, antispasmodics may be effective in the relaxation of the smooth cervical muscle mass, facilitating dilation of the cervix during the first stage of labour. Hyoscine butylbromide is an antispasmodic drug with a rapid onset.[18] Studies have found a statistically significant reduction in the duration of the first stage of labour and shortening of the total duration of labour when using spasmolytics compared with placebo, whereas no effects on the respective durations of the second and third stages of labour have been found. A recent randomised controlled trial (RCT) found that one intravenous dose of 20 mg hyoscine butylbromide was not superior to placebo in preventing slow labour progress in a Norwegian sample of 249 first-time mothers at risk of prolonged labour.[19] However, there are few studies from high-income settings that have examined the effect of hyoscine butylbromide after induction of labour, and no studies have examined repeated doses of hyoscine butylbromide. In the abovementioned study, 249 pregnant participants were treated without serious adverse events (SAEs). The drug reaches maximum effect within 20–30 min and has a half-life of approximately 5 hours.[20]

Sodium bicarbonate counteracts lactate accumulation and reduces acidosis during exercise and has been associated with increased performance in endurance athletes.[21] A Swedish RCT found that administration of sodium bicarbonate to nulliparous women with labour dystocia reduced amniotic fluid lactate and increased the rate of spontaneous delivery compared with standard treatment (84% vs 68%), a difference driven by a reduction in the instrumental delivery rate.[22] An Iranian RCT including nulliparous women found that sodium bicarbonate shortened time to delivery compared with standard care by reducing the duration of first and second stages of labour, with a significantly higher spontaneous delivery rate and lower rate of instrumental delivery in the sodium bicarbonate group.[23] However, these trials were not blinded and did not specifically target women with induction of labour. As to safety, prior studies using 4.26 g of sodium bicarbonate dissolved in water have reported no adverse effects.[23] Among athletes, a recommended dose of 0.3–0.5 g/kg indicates higher doses enhance performance.[24]

As yet, no rigorous RCTs have evaluated the effect of hyoscine butylbromide and/or sodium bicarbonate on delivery mode, and to the best of our knowledge, no study has combined the two drugs in women with induction of labour. The rationale of this double-blind four-arm placebo-controlled randomised trial is therefore to assess the efficacy of oral sodium bicarbonate and intravenous hyoscine butylbromide on facilitating spontaneous (ie, non-operative) delivery in nulliparous women with induction of labour. In addition, we will evaluate the efficacy of the study interventions on patient-reported outcome measures, including birth experience measured by the validated Childbirth Experience Questionnaire (CEQ).[25]

Choice of comparators

The SAINT study has a 2×2 factorial design where three active treatment arms are compared with double-placebo.

Hypothesis and objectives

The main objective of this trial is to establish the superiority of oral sodium bicarbonate combined with intravenous placebo, oral placebo combined with intravenous hyoscine butylbromide and oral sodium bicarbonate combined with intravenous hyoscine butylbromide over double-placebo (ie, oral placebo combined with intravenous placebo) with respect to spontaneous (ie, non-operative) delivery. For each of the three comparisons, the null hypothesis is defined as no difference between the active treatment group and the double-placebo group (reference group) with respect to the outcomes in question.

METHODS AND ANALYSIS

SAINT trial design

We have chosen the RCT design to determine causal effects between intervention and outcome. The 2×2 factorial design, where three active treatment arms are compared with double-placebo, will allow us to test two drugs concurrently and assess whether there are synergistic effects between them.

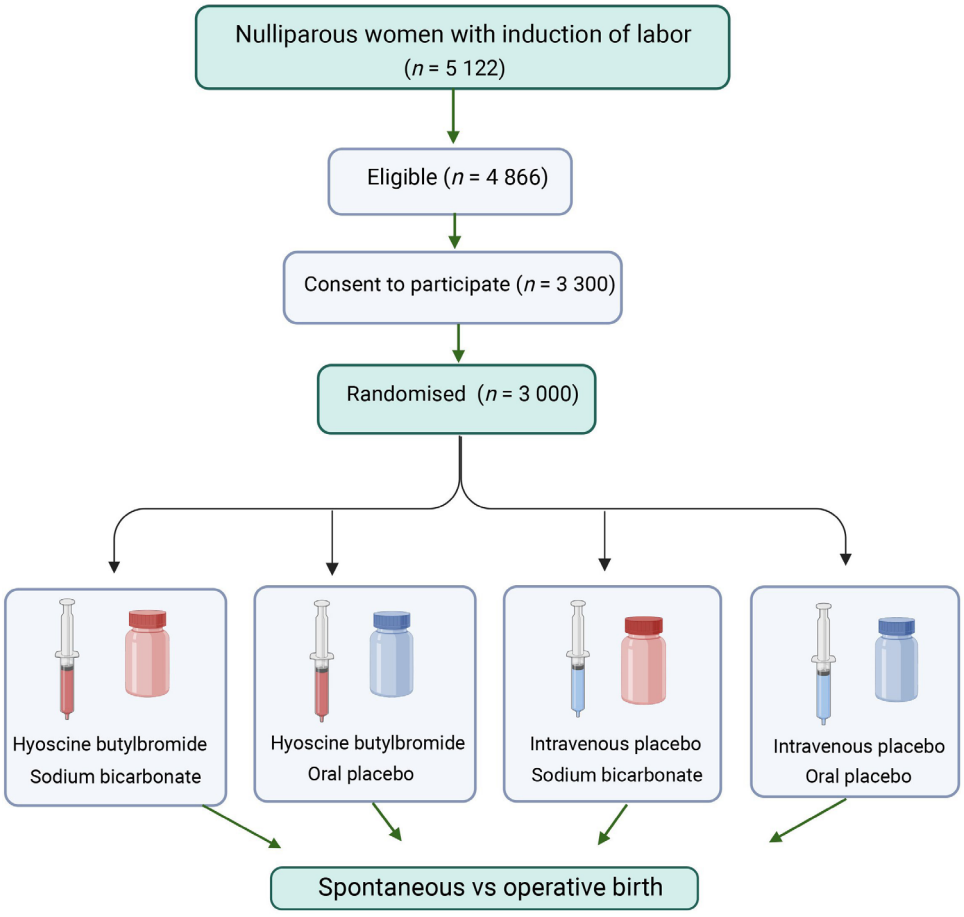

Figure 1 Safe Induction of Labour Trial study participant enrolment and the four-arm study design. Numbers of screened and eligible participants were estimated prior to study start. Created with BioRender.com.

Study setting and registration

This is a nationwide study recruiting women from 10 delivery departments in all four health regions in Norway. All included units provide universal healthcare with comprehensive emergency obstetric care and have annual birth numbers >1000. In total, the 10 units account for around 65% of annual births in Norway.[26] The Safe Induction of Labour Trial (SAINT) study is registered in EudraCT (2021-000392-37), approved 27 November 2020, and in EUCT (2024-511848-55-00). The study protocol is registered at http://clinicaltrials.gov (ClinicalTrials.gov ID: NCT05719467). The Trial Protocol (V.9) was updated on 21 June 2024 (online supplemental material A).

Patient enrolment and eligibility criteria

The plan for enrolment is outlined in figure 1. The study will recruit and include nulliparous women where induction of labour has been decided. Inclusion and exclusion criteria are listed in table 1.

All pregnant women at the participating sites are informed of the study at booking. When induction of labour is decided, women are screened for eligibility, and written and oral information about the study is provided. Informed consent is obtained from the participant before the onset of labour (online supplemental materials B and C). Biochemical tests are performed to uncover participants with previously undetected kidney and/or liver failure or severe electrolyte disturbance. A blood sample (EDTA whole blood) is secured for biobanking. After delivery, the participant's partner is asked for consent to use health information about the newborn.

Methods for induction of labour

Choice of method of induction of labour is based on standard care, that is, decided on according to national and/or locally adapted guidelines. The Norwegian national guidelines recommend sequential induction, initiated with a Foley/balloon catheter in the case of an unripe cervix (Bishop score≤7) for 12–48 hours followed by oral or vaginal misoprostol for 24–48 hours, with artificial rupture of membranes and/or oxytocin at the discretion of the attending health staff.[27] The national guidelines were revised in 2020. Prior to the study start in the beginning of 2023, an alignment process was conducted in 2021–2022, involving all participating delivery units to encourage homogeneity in method choice and sequence.

Interventions

The study intervention is outlined in table 2. The intervention period is defined by the start of labour, that is, a cervical dilation of 4 cm or more with regular uterine

Table 1 Inclusion and exclusion criteria in the Safe Induction of Labour Trial study

Inclusion criteria	Exclusion criteria
18–50 years Pregnant, nulliparous, ≥ 37 weeks of gestation, carrying a live fetus in cephalic presentation Fulfilling criteria for induction of labour Decision to induce labour has been made Capable of understanding study information and giving signed informed consent, including compliance with the requirements and restrictions listed in the informed consent form	Multiple gestation Scheduled elective caesarean section Spontaneous start of labour Known maternal intestinal stenosis, ileus or megacolon; maternal myasthenia gravis; untreated glaucoma Persisting maternal tachycardia (HR>130 bpm) > 30 min Persisting fetal tachycardia (ie, fetal HR baseline>170 bpm) > 30 min Maternal hypersensitivity to ingredients in IMP (hyoscine butylbromide, sodium bicarbonate or sodium chloride) Maternal heart disease with HR monitoring during labour Prenatal diagnosis of fetal heart gastrointestinal disease Maternal severe hyponatraemia (<125 mmol/L) or severe hypokalaemia (<2.5 mmol/L) Maternal moderate/severe kidney failure* or maternal elevated serum creatinine (> 110 µmol/L) Maternal elevated ALAT>100 U/L Participation can still be considered for participation with ALAT>100 U/L if explained by obstetric cholestasis or HELLP syndrome

*Stages III–V: glomerulus filtration rate <59 mL/min/1.73 m^2.
ALAT, alanine aminotransferase; BPM, beats per minute; HELLP, haemolysis, elevated liver enzymes, and low platelet count; HR, heart rate; IMP, investigational medicinal product.

contractions. The investigational medicinal product (IMP) doses 1–3 are provided by the attending midwife at the time points noted in the schedule of activities (SoA). Treatment is given every 4 hours throughout the first and second stages of labour (limited to 8-hour duration and maximum three doses of IMP). If delivery is imminent (delivery expected within 30 min and/or the presenting fetal part at station 3+ in the maternal pelvis with normal labour progress), further IMP doses are suspended.

The participants are allocated to one of four study arms, where each IMP dose consists of either:

1. 20 mg (1 mL, 20 mg/mL) of intravenous hyoscine butylbromide and 4 g (four tablets, 1 g each) of oral sodium bicarbonate
2. 20 mg (1 mL, 20 mg/mL) of intravenous hyoscine butylbromide and matching oral placebo (four tablets, identical to the sodium bicarbonate tablets in terms of taste, smell, and appearance)
3. 1 mL of intravenous placebo (0.9% sodium chloride) and 4 g (four tablets, 1 g each) of oral sodium bicarbonate
4. 1 mL of intravenous placebo (0.9% sodium chloride) and oral placebo (four tablets, identical to the sodium bicarbonate tablets in terms of taste, smell, and appearance).

All IMP doses are prepackaged in one sealed kit for each participant. Sodium bicarbonate with matching placebo tablets are manufactured by Kratab AS, as described in the Chemical and Pharmaceutical Quality Documentation (11 March 2021) attached to the application to the Norwegian Medical Products Agency. Hyoscine butylbromide produced by Sanofi-Aventis is used, as described in the Summary of Product Characteristics.[20] Intravenous sodium chloride produced by Dyckerhoff Pharma GmBH & Co. KG, Köln, Germany, is used as intravenous placebo. Cervical dilation and vital signs of mother and fetus are checked according to the time points summarised in the SoA. Pain intensity is reported by the woman using the verbal numerical rating scale (VNRS) at the time points noted in the SoA. Fetal surveillance in labour is conducted with cardiotocography and adjunctive methods like ST segment analysis or fetal scalp lactate, according to local guidelines. Criteria/indications for obstetric intervention during labour are decided according to local guidelines. Participants receive standard obstetric care regardless of the study arm to which they have been allocated. Such interventions include, but are not limited to, labour augmentation with oxytocin, epidural and/or pudendal analgesia, vacuum or forceps delivery and caesarean section. The primary indication for operative intervention (instrumental delivery or caesarean section) is recorded according to local definitions. Measurements of neonatal status include umbilical cord pH, Apgar score and transfer to the neonatal intensive care unit.

Outcomes

The objectives and corresponding primary and secondary outcomes in the SAINT study are described in table 3.

As part of the secondary objectives, we will evaluate the effect of the study interventions on birth experience, measured by the validated CEQ four to 6 weeks after delivery.[25] The response format is a 4-point Likert scale with the following response options: 1 (totally agree), 2 (mostly agree), 3 (mostly disagree) and 4 (totally disagree). Memory of labour pain and sense of security and control will be assessed with the VNRS, ranging from 1 to 10. The VNRS is easy to administer and score and a recognised unidimensional measure of pain.[28]

Table 2 Schedule of activities

	Baseline (induction)	Intervention period (labour and delivery)							Post-intervention (maternity ward)
Procedure	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
Time	**Induction**	**Start labour IMP dose 1**	**30 min after IMP dose 1**	**IMP dose 2**	**30 min after IMP dose 2**	**IMP dose 3**	**30 min after IMP dose 3**	**Delivery**	**Before discharge**
Written information about the study	X								
Informed consent and inclusion	X								
Medical history/current conditions	X								
Maternal physical examination	X								
Examination of fetal position and presenting part	X	X							
Randomisation		X							
Laboratory tests*	X								
Blood sample†	X								
Vital signs fetus	X	X	X	X	X	X	X		
Vital signs mother	X	X	X	X	X	X	X	X	X
Cervical dilation	X	X		X		X			
Study intervention		X		X		X			
Pain verbal numerical rating scale		X	X	X	X	X	X		
Adverse event review		←	—	—	—	—	—	—	→
Serious adverse event review		←	—	—	—	—	—	—	→
Neonatal status								X	
Neonatal physical exam									X

*Laboratory tests include haemoglobin, platelet count, creatinine, sodium, potassium and alanine aminotransferase.
†Whole blood for biobanking.
IMP, investigational medicinal product.

Table 3 Objectives and primary and secondary outcomes in the Safe Induction of Labour Trial study

Objectives	Outcomes
Primary	
To assess the efficacy of oral sodium bicarbonate and intravenous hyoscine butylbromide on facilitating spontaneous delivery in participants with induction of labour	► Spontaneous delivery (ie, no instrumental delivery, no caesarean section) vs operative delivery
Secondary	
To assess the efficacy of oral sodium bicarbonate and intravenous hyoscine butylbromide on	
► Duration of labour	► Duration from first IMP administration to delivery ► Duration from first IMP administration to 10 cm cervical dilation ► Mean cervical dilation rate from first IMP administration to 10 cm cervical dilation ► Duration of labour from onset of active labour to delivery ► .
► Operative delivery	► Vaginal delivery (instrumental or spontaneous) vs caesarean section ► Mode of delivery (spontaneous delivery, instrumental delivery or emergency caesarean section)
► Amount of oxytocin administered to augment contractions	► Amount of oxytocin administered, measured as total time of oxytocin infusion (min) and total amount of oxytocin (IU), calculated based on standardised concentration of the infusion solution
► Pain during labour	► Change in pain score from before each IMP administration to 30 min after IMP administration using the verbal numerical rating scale (0–10)
► Blood loss at delivery	► Postpartum haemorrhage>500 mL ► Postpartum haemorrhage>1000 mL ► Postpartum haemorrhage>1500 mL ► Blood transfusion
► Episiotomy	► Episiotomy
► Anal sphincter injury	► Anal sphincter injury, defined as obstetric anal sphincter injury of grade 3 or 4
► Postpartum urinary retention	► Need for postpartum catheterisation
► Fetal cardiotocography effects	► Fetal cardiotocography changes during labour
► Neonatal outcomes	► Apgar score<7 at 5 min and 10 min ► pH<7.00 and <7.10 in umbilical artery and pH<7.20 and < 7.35 in umbilical vein ► pH in umbilical vein ► pH in umbilical artery ► Admission to the neonatal intensive care unit
► Patient-reported outcome measures	► Birth experience measured by the validated Childbirth Experience Questionnaire

IMP, investigational medicinal product.

Medical resource utilisation and health economics data (patient-reported outcome measures) will be collected by the investigator and site personnel for all participants throughout the study and reported by the participants in follow-up questions in the CEQ. The data collected will include information on duration of hospitalisation, including duration by wards and duration of partner's sick leave following discharge of the participant, and may be used to conduct exploratory economic analyses.

Sample size calculation and recruitment

This trial is primarily designed to establish superiority of active treatment over double-placebo in increasing the rate of spontaneous delivery. As the primary outcome is dichotomous (spontaneous delivery vs operative delivery), the sample size calculation was based on a two-sample test of proportions. To correct for the multiple pairwise comparisons between the three active treatment groups and the double-placebo group, a Bonferroni correction was applied by dividing the overall significance level of 0.05 by 3. The statistical power was set at 0.80. Approximately 56% of all deliveries at term by induced nulliparous women with a singleton pregnancy and cephalic presentation result in spontaneous delivery.[15] A relative risk of 1.15 between an active treatment group and the

double-placebo group, corresponding to a 15% increase in spontaneous delivery in the active treatment group, is considered clinically significant. Detection of such a treatment difference requires 710 women in each group. Hence, a total of 2840 (710×4) women are required when using an allocation ratio of 1:1:1:1 (ie, equal sample sizes of the treatment groups). Based on previous annual induction numbers, approximately 5100 women will be screened to achieve 3000 participants randomly assigned to one of the study arms, taking potential drop-out and non-compliance into account.

Randomisation

On day 0, participants will be assigned the lowest randomisation number available at the respective sites. The randomisation number encodes the participant's assignment to one of the four study arms according to the randomisation schedule generated prior to the trial by the Clinical Trials Unit at Oslo University Hospital. A blinded IMP kit labelled with a unique randomisation number will be allocated to each participant and handled by the designated midwife.

Blinding/masking

Allocation to treatment will be masked for the participants, care providers, investigators and outcome assessors.

Criteria for discontinuation or modifying allocated interventions

The following discontinuation criteria have been defined:

1. Maternal serious skin reaction, including Stevens-Johnson syndrome.
2. Anaphylactic reaction or shock.
3. Serious maternal non-sinus cardiac rhythm or tachycardia (heart rate>130 for > 30 min).
4. Serious persisting fetal tachycardia (baseline fetal heart rate>170 for >30 min).
5. Maternal continuous vomiting without effect of intravenous fluids and antiemetic drugs.

In rare instances, it may be necessary for a participant to discontinue study intervention, in which case she will still be included in the safety analyses of possible side effects.

Data management

At each site, data are recorded in electronic medical records in real time by the care provider. Clinical trial data, including outcomes, will be recorded in the electronic case report form (eCRF) in Viedoc (www.viedoc.com). All data management, preliminary data compilation and data storage are conducted in Viedoc. The data management procedures are performed in accordance with the Norwegian Clinical Research Infrastructures Network guidelines.[29]

Statistical methods

The following analysis sets will be considered:

- Intention-to-treat (ITT) set: all randomised trial participants with a signed informed consent, regardless of protocol adherence.
- Full analysis (FA) set: all eligible trial participants in the ITT set who have received at least one IMP dose.
- Per-protocol (PP) set: all eligible, randomised trial participants with a signed informed consent who have followed the protocol with no major protocol deviations and received the same IMP to which they have been randomised.
- Safety set: all trial participants who have received at least one IMP dose, including ineligible and non-randomised participants and participants who later revoke their informed consent.

The main efficacy analysis of each outcome will be based on the FA set. Sensitivity analyses based on the ITT and PP sets will also be conducted for comparison reasons. Safety analyses will be based on the safety set.

Patient demographics and baseline characteristics will be summarised by study arm. The primary outcome will be analysed using binary logistic regression, and the results will be presented as marginal adjusted risk differences between each of the three active treatment groups and the double-placebo group. Analyses of secondary outcomes will be regarded as supportive. Dichotomous variables and categorical variables with more than two levels will be analysed using binary and multinomial or ordinal logistic regression, respectively. Continuous variables will be analysed using linear or median regression. Time-to-event variables will be analysed using an appropriate survival analysis method such as Weibull or Cox regression. Safety analyses will be limited to descriptive statistics and tabulations.

To judge whether the study should be terminated early due to clear evidence of efficacy of any of the two study drugs, an interim analysis of the primary outcome is conducted after the inclusion of two-thirds of the total sample size (2000 women). In this analysis, the efficacy of the three active treatments with respect to increasing the spontaneous delivery rate is tested using a Bonferroni-corrected significance level equal to an overall significance level of 0.001 divided by 3, which is the number of pairwise comparisons between the three active treatment groups and the double-placebo group.

All efficacy analyses will be presented with the point estimate of the relevant effect measure of the treatment difference, the associated two-sided 95% CI, and the p value of the corresponding two-sided hypothesis test. In the final analysis, the p values are compared with a Bonferroni-corrected significance level to account for the multiple pairwise comparisons between treatment groups and assure an overall significance level of 0.05. The Bonferroni-corrected significance level for the hypothesis tests of the primary outcome also takes into account the so-called alpha spending in the interim analysis.

Prior to the final analysis, the database will be locked for further entering and altering of data. A separate statistical analysis plan will be finalised, signed and dated prior to database lock and unblinding. The treatment allocation will be revealed after database lock and used in the statistical analysis.

Data will be analysed using Stata for Windows (StataCorp LLC) and R for Windows (R Foundation for Statistical Computing).

Data monitoring and auditing

A data monitoring committee (DMC) was established before the inclusion of the first participant and has three members: a statistician, a medical doctor and a midwife. The DMC will evaluate the safety and interim analyses, including the critical effectiveness endpoint, and will recommend to the sponsor whether to continue, modify or stop the study according to the DMC Charter.

Adverse events and assessment of harm

Adverse events (AEs), including SAEs, will be reported by the participant or, when appropriate, a caregiver or partner/birth companion. The investigator and any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE and remain responsible for following up all AEs that are considered related to the study intervention or study procedures or caused the participant to discontinue the study intervention. All AEs are collected from the first IMP administration until 24 hours after the last IMP administration or at discharge, as specified in the SoA. All SAEs are reported to the medical monitor as soon as possible.

Emergency unblinding

Unblinding of the treatment allocation is permissible only if the safety and well-being of the participant is compromised. In the event of an SAE, the principal investigator (PI) or the attending physician on duty may break the treatment code, as found in sealed envelopes at the sites, only if the appropriate consecutive management of the patient necessitates immediate knowledge of the current treatment (eg, severe anaphylactic reactions).

Study management

The coordinating PI and coinvestigators are responsible for appropriate staff training and task allocation. The investigators are responsible for giving the participating women full and adequate verbal and written information about the purpose, nature, possible risks and possible benefits of the study. The coordinating PI has insurance coverage for this study through membership of the Norwegian Drug Liability Association.

Study monitoring

The study is supervised by external monitoring. The Clinical Trials Unit at Oslo University Hospital is responsible for study monitoring. The study monitors perform reviews every 6 months throughout the study period, while both clinical data managers and study monitors may remotely and proactively monitor the eCRFs to improve data quality.

Patient and public involvement statement

The SAINT study group consortium include a number of collaborators and users. Core users have included the head of the user group at the Division of Obstetrics and Gynaecology at Oslo University Hospital and professional societies. Users have commented on the study design, research questions and questionnaire development. Users will participate during the scientific process and report writing. Users may be co-authors of papers if Vancouver criteria are fulfilled. Optimal mechanisms for transfer of intervention results and resulting new knowledge to policymakers, health professionals and other researchers are to be determined.

ETHICS AND DISSEMINATION

Research ethics approval, protocol amendments and consent

The study protocol is approved by the Regional Committee for Medical and Health Research Ethics South East Norway B (reference 235247[23]) and European Union Clinical Trials (reference 2024-511848-55-00). The study is also approved by the Norwegian Medical Products Agency (reference 21/06793-3). The results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results. The results of this study will also be submitted to the competent authority and the Regional Ethics Committee for Medical and Health Ethics South East Norway according to Norwegian and EU regulations.

Confidentiality

Personal information about potential and enrolled participants will be stored in secure digital and physical localities in line with regulations of the Institutional Review Boards.

Access to data

The PI, co-investigators, trial statistician and data manager will have access to the final data set. Prior to publication on the primary and secondary outcomes, the data manager will have access to the full data set. The data manager will verify any problems in the data by consulting the PI, coinvestigators and trial statistician when necessary. After completion, the data manager and trial statistician will finalise the data set for statistical analysis.

Ancillary and post-trial care

No ancillary or post-trial care is planned.

Dissemination policy

Results of this study, including potential null findings, will be published in peer-reviewed journals and presented at national and international scientific meetings.

DISCUSSION

The SAINT study is designed to assess the efficacy of adjuvant treatment on the rate of spontaneous delivery in nulliparous women with induction of labour. Operative

delivery (ie, instrumental delivery or caesarean section) is highly prevalent after induction of labour and related to several serious maternal and fetal complications. To achieve safer births after induction of labour, efforts to reduce operative delivery are encouraged. The primary objective of the SAINT study, which is to assess the efficacy of the study interventions on the rate of spontaneous delivery, is therefore clinically relevant. An increase in the rate of spontaneous delivery of 15% compared with double-placebo is considered clinically significant.

Both hyoscine butylbromide and sodium bicarbonate have been used in previous studies involving women in labour without reported SAEs. In this study, we plan three doses of IMP in total during labour, which involves both a higher number of doses and a higher total drug dose than in previous studies. In our study, hyoscine butyl bromide is administered intravenously at a dose of 1 mL (20 mg/mL). This aligns with the recently published RCT assessing the effect of hyoscine butyl bromide on labour duration,[19] where 249 pregnant participants were treated without SAEs. While a 40 mg dose has indicated greater efficacy in shortening labour, studies involving 218 women report no increase in side effects compared with placebo, deeming multiple doses safe.

Regarding sodium bicarbonate, the proposed regimen in our study of 4 g, repeatable twice at 4-hour intervals, equals 0.07 g/kg for a 60 kg woman—far below athletic recommendations. With onset in 15 min and a 1–3-hour duration, this dosage keeps risks low. Overall, our chosen doses for both substances are deemed safe.

The study includes 10 different departments across Norway and many health workers (both midwives and medical doctors). An important task for the study coordinators will therefore be to assure that the local PIs educate the local health workers and secure proper education and information about the study and the two study medications. Considering the measures taken to minimise risk to the participants in this study, the potential risks identified in association with the administration of hyoscine butylbromide and sodium bicarbonate are justified by the anticipated benefits to the participants.

Study strengths and limitations

This study includes a vulnerable group of women about to give birth with a complicated pregnancy and an indication for induction of labour. We argue that including such participants in research studies is the only way of improving labour care. The study design has been discussed with the user group at the Division of Obstetrics and Gynaecology, Oslo University Hospital, and with the PIs at the different sites. The user group's suggestions included use of patient-reported outcome measures, dissemination of information about the study early in pregnancy and assessment of the fetal effects of IMP administration. These suggestions have been added to the study protocol and implemented as part of the study. The four-arm study design may increase the complexity of a clinical trial; however, we argue that this design is required to assess the possible synergistic effects between the two study drugs. To meet the challenge of complexity, we use prepackaged blinded IMP kits and put emphasis on rigorous continuous training of study personnel. A potential study limitation in relation to the effect of sodium bicarbonate is that we do not measure lactate levels in the amniotic fluid before and after IMP administration due to difficult logistical and cost implications. The study is limited to nulliparous participants; hence, the results will not be generalisable to multiparous women.

Status and timeline of the study

The study started on 5 January 2023, with a planned 28-month inclusion period at 10 delivery units across Norway. The end of study is defined as the last visit of the last participant, that is, when the CEQ has been received, but no later than 6 months after the last patient is included.

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