PROCEED Study Protocol

1. Original Study Protocol (January 6, 2016)
2. Final (V2) Study Protocol (September 28, 2018) with changes noted on title page.

Effect of a Patient-Centered Decision App on TOLAC: An RCT

The PRiOr CEsarEan Decision App (PROCEED) Study

Sponsored by:
US National Institute of Health
Grant #1R01HD078748
January 6, 2016

IRB Approvals
UCSF/Marin Community Clinic: CHR #13-11707
Massachusetts General Hospital: IRB #2015P002284
Northwestern University Medical Center: IRB #STU00104496

NCT02646423

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PERSONNEL AND DUTIES

Principal Investigator (PI)

The PI is experienced in all aspects of the design, conduct and oversight of randomized controlled trials and prospective studies at multiple clinical sites and is an expert in the fields of medical decision-making, preference (utility) measurement, and decision-assisting tool creation and evaluation. The PI will take a lead role in all aspects of the proposed project, working with the site PIs, other co-investigators, and staff members to ensure timely and accurate completion of the project. The PI will direct day-to-day activities and provide overall governance and scientific leadership to the study.

Statistician Co-investigator

The statistician co-investigator will direct analysis strategy for study design and manuscript preparation. The statistician will also oversee data analysis by the analyst and advise the PI and other co-investigators on methodological issues.

Site Principal Investigator (site PIs)

The site PIs will meet monthly by phone and biannually in person (along with the other co-investigators) to contribute to the overall study design and ensure each site is executing the study as prescribed. Site PIs are responsible for hiring and training site staff and will provide clinical and research expertise in the design and implementation of study instruments and protocols. Site PIs will monitor study enrollment and troubleshoot any recruitment issues as needed. They will also assist with chart review for participant delivery outcomes.

Other Co-investigators

Additional co-investigators will join the monthly calls and biannual in-person meetings. They will support patient recruitment from the obstetric practices at each site and will provide clinical input into data analyses and manuscripts for submission to peer-reviewed journals. They will also assist with chart review for participant delivery outcomes.

Project Manager

The project manager is responsible for the overall operations of the study, including managing recruitment and enrollment, guiding IRB submissions, and scheduling and preparing agendas for investigator and coordinator meetings. The project manager will monitor project timelines and ensure recruitment goals are met and recruitment and data collection are carried out per established protocols. The project manager will document any revisions to protocols and surveys and acquire IRB approvals as needed. The project manager will also work with the data manager/statistical analyst to design and implement study databases.

Data Manager/Statistical Analyst

The data manager/statistical analyst is responsible for creating and managing all databases for the project, monitoring data quality, and conducting data cleaning and statistical analyses under the direction of the statistician co-investigator and PIs.

Research Coordinators/Interviewers

The Research Coordinators (RCs) are the primary administrative points of contact for the study. They will prepare and submit all materials for IRB approval including the initial application, renewals, and all modifications. They will pilot and fine-tune study instruments; screen, consent, and interview participants; randomize participants per protocol; abstract medical data from

charts; and distribute participant remuneration. They will be responsible for following the guidelines for study operations outlined in this protocol and will email the UCSF project manager in the event of any protocol violations (e.g., mis-randomization, erroneous inclusion of subjects in the study, breach of confidentiality). They will participate in weekly or biweekly conference calls with the project manager and one or more PIs to go over recruitment and data collection activities and targets.

STUDY SCHEMA

Purpose: To assess the effect of the PROCEED Prior Cesarean Decision Support app (versus usual care without the app) on rates of trial of labor after cesarean (TOLAC) among pregnant women with a prior cesarean delivery (CD).

Design: This is a two-armed randomized controlled trial (RCT) among 1,320 English- or Spanish-speaking pregnant women (1:1 randomization sequence for the intervention).

Study Population: Pregnant women receiving prenatal care at a participating healthcare facility. Women will be eligible to enroll if they meet all of the following criteria.

Inclusion criteria:

- Between 12 weeks 0 days and 24 weeks 6 days gestation at enrollment
- Speak English or Spanish
- Have had one and only one prior CD
- Prior low transverse cesarean
- Unknown scar but TOLAC eligible

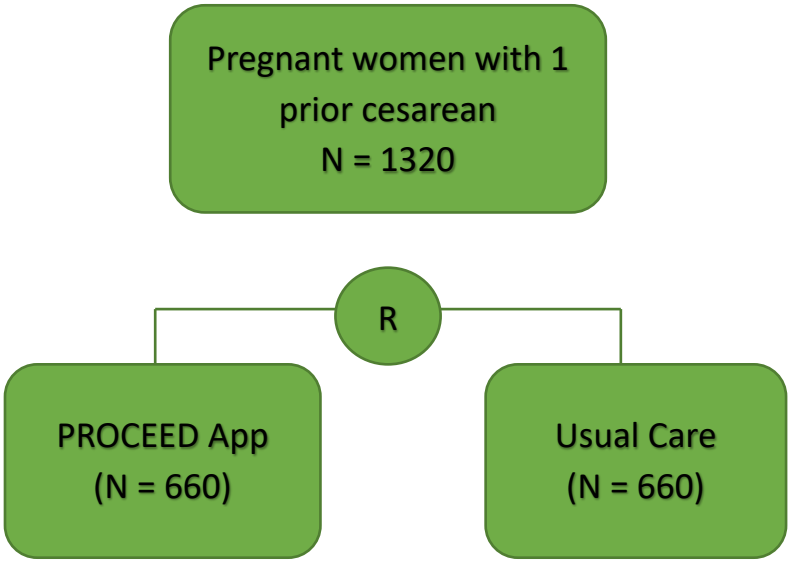
Exclusion criteria:

- No prior cesarean delivery, or more than one
- Multiple gestation pregnancy
- Prior vaginal birth after cesarean
- Any contraindications to TOLAC (prior classical cesarean, prior uterine surgery, T-incisions, other contraindication)
- Delivering at outside institution

Study Size: The recruitment goal is 1,320 participants, for a recruitment rate of 40 participants per month and a final subset of 627 per arm (1254) projecting 5% loss to follow up.

Study Intervention:	Participants in the intervention arm will be provided with the PROCEED Prior Cesarean Decision app, which includes approximately 15 minutes of dynamic web-based informational content including potential maternal and neonatal complications from vaginal and cesarean deliveries, values clarification questions, and individualized estimates of likelihood of successful TOLAC.
Study Duration:	Data collection start date: January 2016 Estimated data collection end date: July 2019
Primary Hypothesis:	Compared to women who receive usual care only, women who are randomized to use the Prior Cesarean Decision app will be more likely to undergo TOLAC.
Secondary Hypotheses:	Compared to women who receive usual care only, women randomized to use the Prior Cesarean Decision app will: 1. be more likely to have a vaginal birth after cesarean (major secondary outcome) 2. be more knowledgeable about TOLAC and elective repeat cesarean delivery (ERCD) and their potential outcomes 3. experience less decisional conflict 4. report higher levels of shared decision making regarding delivery approach 5. report higher levels of decision self-efficacy 6. report higher levels of decision satisfaction 7. experience lower rates of maternal and neonatal morbidities
Study Sites:	University of California, San Francisco Marin Community Clinic Massachusetts General Hospital Northwestern University Medical Center

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



1.0 INTRODUCTION

1.1. Background and Prior Research

Public health impact of cesarean rate in the US. Cesarean delivery (CD) is the most common inpatient surgery in the US, accounting for nearly one third of births annually. In the last decade, the CD rate has increased by approximately 50%, with almost 1.3 million procedures performed in 2012.[1] Moreover, at $7.8 billion annually, these deliveries account for almost half of childbirth-related expenses of hospitalization.[2] CDs have been associated with an increase in major maternal morbidity,[3–5] with corresponding increases in length of inpatient care following delivery and frequency of hospital readmission.[6] Organizations including Healthy People[7], the American College of Obstetricians and Gynecologists (ACOG)[8], and the American College of Nurse Midwives[9] have targeted reducing the CD rate as an important public health goal for more than a decade; however, identifying interventions to achieve this goal has proven challenging.

Causes and consequences of the rising rate of repeat cesareans. Repeat CDs are a significant contributor to the increased cesarean rate, resulting from the combination of a rising rate of primary CD and a decreasing rate of vaginal birth after cesarean, which declined from a high of 28.3% in 1996[2] to 9.2% in 2010.[10] Why the VBAC rate has decreased so dramatically remains a subject of debate. Numerous medical and nonmedical factors have been posited as contributing to this decline, including the decreasing number of hospitals willing to provide this option and the diminishing number of obstetric providers who offer this approach. In addition, a substantial portion of the decrease is related to women foregoing trial of labor after cesarean (TOLAC) even though their hospitals and obstetricians provide the opportunity. For example, among hospitals in the NICHD Maternal-Fetal Medicine Units network, TOLAC rates declined from 51.8% to 29.8% ($p<.001$) from 1999-2002, even though TOLAC continued to be offered at all sites.[11] In a study of "good TOLAC candidates" at a 14-hospital network where TOLAC was available, the average TOLAC rate was only 30%.[12] And at Northwestern, one of the clinical sites for our study,

TOLAC rates decreased by two-thirds from 1995 to 2010 although all providers offer this labor approach.

Importantly, the declining VBAC rate is *not* primarily due to new and more concerning information about the risks of TOLAC; recent epidemiologic studies have demonstrated that the core population-level outcomes of TOLAC, such as the chance of VBAC or of uterine rupture if a TOLAC is attempted, are no different today than they were three decades ago.[2,13–15] Similarly, this decline is not primarily due to changes in characteristics of the population that would make VBAC less likely if TOLAC is undertaken; these decreases in TOLAC have affected all women, regardless of their probability of VBAC or risks of adverse TOLAC outcomes.[11] The extent to which these changes are driven by patient preferences is not known. Data from qualitative studies offer some insight, but the value of that information is limited by the non-generalizability of the study populations and the lack of quantitative analyses.[16–21] Furthermore, while decreased TOLAC rates are occurring throughout the US, there are persistent, unexplained racial/ethnic, geographic, and socioeconomic differences in rates of TOLAC and VBAC.[22] This variation, in the absence of a demonstrated basis in clinical science or patient preferences, raises concern about the efficiency, effectiveness, and patient-centeredness of approach to delivery after CD.[23]

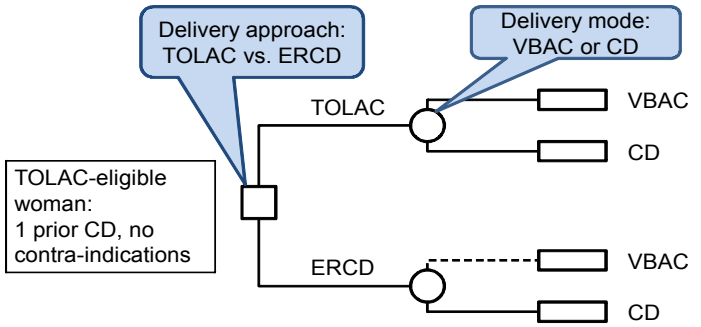


Figure 1. Delivery approach versus delivery mode. For women who are eligible for trial of labor after cesarean (TOLAC), a decision regarding the **delivery approach (**whether to schedule an **elective repeat cesarean delivery (ERCD)** or to undergo **TOLAC)** is made. The TOLAC rate is the percentage of eligible women who undergo a TOLAC (versus an ERCD). If TOLAC is chosen, the ultimate **delivery mode (VBAC or CD)** is uncertain. Most, but not all, women who plan an ERCD will deliver via CD.

Call to action. An NIH consensus conference statement noted that "the informed consent process for TOLAC and ERCD should be evidence-based, minimize bias, and incorporate a strong emphasis on the values and preferences of pregnant women," and recommended "interprofessional collaboration to refine, validate, and implement decision-making and risk assessment tools" to accomplish that goal.[22] Given the broad policy support for shared decision making in this context,[22,24] the large absolute number of women facing the choice of TOLAC, and the short- and long-term consequences of this decision for mothers and babies, an intervention aimed at informing patients and helping them articulate their preferences could lead to improvements in the decision making process and have a significant impact on the health of individuals and the health care system.[25,26] Our overarching goal is to create and evaluate a tool to help TOLAC-eligible women delivering at hospitals that offer TOLAC consider individualized risk assessments, incorporate their values and preferences, and participate in a shared decision making process with their providers to make informed decisions about delivery approach. We believe this improved informed decision making process will lead to increased TOLAC.

Our prior studies of decision making. In a recently completed randomized study (R01 HD049686), PI Kuppermann and colleagues found that women who used a prenatal testing decision tool had significantly lower uptake of invasive diagnostic testing, greater knowledge

about testing and birth defects, and better comprehension of the risks of amniocentesis or chorionic villus sampling.[27] We believe the PROCEED study also has the potential to generate an evidence-based intervention that may lower the overall CD rate among diverse populations of women, a critical yet elusive goal in obstetric care. Moreover, because the Prior Cesarean Decision app will make explicit the probability of achieving VBAC, it is expected that the group of women who undertake TOLAC after using the decision app will be enriched with those who are more likely to succeed in their attempt. As over 90% of morbidity occurs in women who undertake TOLAC but ultimately have a cesarean during labor[28], this app may also lower the rate of CD without increasing either maternal or perinatal morbidity.

2.0 STUDY HYPOTHESES AND DESIGN

2.1. Primary Hypothesis

The primary hypothesis of this study:

- Compared to women who receive usual care only, women who are randomized to use the Prior Cesarean Decision app will be more likely to undergo TOLAC.

2.2. Secondary Hypotheses

The secondary hypotheses of this study are:

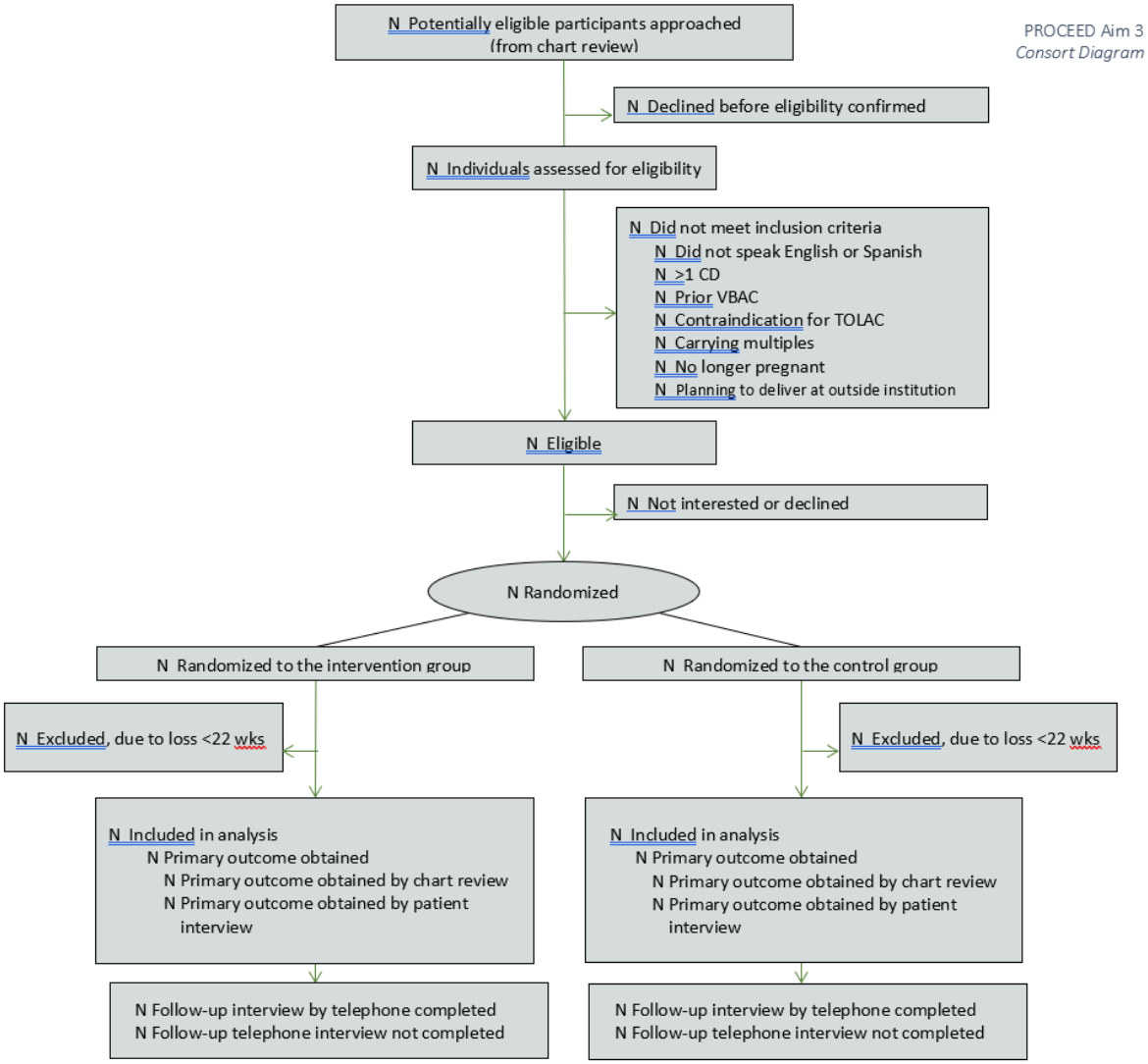
- Compared to women who receive usual care only, women randomized to use the Prior Cesarean Decision app will:

1. be more likely to have a vaginal birth after cesarean (VBAC) (major secondary outcome);
2. be more knowledgeable about TOLAC and ERCD and their potential outcomes;
3. experience less decisional conflict;
4. report higher levels of shared decision making regarding delivery approach;
5. report higher levels of decision self-efficacy;
6. report higher levels of decision satisfaction; and
7. experience lower rates of maternal and neonatal morbidities

2.3. Study Design

This is a two-armed RCT to assess the impact of a Prior Cesarean Decision app on the delivery outcomes of 1,320 English- or Spanish-speaking women with a prior cesarean delivery (1:1 randomization sequence for the intervention). Following is a consort diagram of the study:

Figure 2. Consort diagram



2.3.1. Timeline

Randomized controlled trial (n=1320)	2016				2017				2018				2019				2020	
	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Sep-Dec	Jan-Mar	Apr-Jun
Recruit RCT																		
Phone follow-up																		
Chart reviews																		
Create databases, enter and clean data																		
Analyze data and prepare manuscripts																		

2.3.2. Randomization

Randomization tables will be generated with SAS v9.4 using the RAND function utilizing the Mersenne-Twister random number generator. To make treatment assignments difficult to anticipate, the program will generate randomly permuted blocks of 8, 10, and 12 in random order. Randomization will be stratified by language (English/Spanish) and recruitment site. Randomization tables will be uploaded into a randomization module in the study database by the data analyst. To protect the integrity of the randomization sequence, RCs will not have access to the randomization tables.

3.0 STUDY POPULATION

A total of 1,320 pregnant women between 12 weeks 0 days and 24 weeks 6 days gestation with one prior cesarean will be enrolled into the study from three distinct geographic areas of the United States. Three sites serve primarily lower income women, with many Spanish speakers. The remaining three sites serve primarily English-speaking communities of higher socioeconomic status.

Participants will be randomized to receive the Prior Cesarean Decision app or usual care, stratified by site and language. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. They will be approached, screened, and enrolled as described in Sections 5.1.1., 5.1.2., and 5.1.3. Issues related to participant retention and withdrawal from the study are described in Sections 3.3 and 3.4, respectively.

3.1. Inclusion Criteria

Women who meet all of the following criteria are eligible for inclusion in the study:

- Prior cesarean delivery
- Between 12 weeks 0 days and 24 weeks 6 days gestation at enrollment
- English- or Spanish speaker
- Prior low transverse cesarean

3.2. Exclusion Criteria

Women who meet any of the following criteria will be excluded from this study:

- No prior cesarean delivery, or more than one
- Multiple gestation pregnancy
- Unable to speak English or Spanish
- Prior VBAC
- Ineligible for TOLAC (due to prior classical cesarean, prior uterine surgery, T-incision, or other contraindication)
- Delivering at outside institution

3.3. Participant Retention

Once a participant enrolls in PROCEED, the study site will make every effort to retain her in the study for the entire follow-up period in order to minimize possible bias associated with loss to follow-up. Components of such procedures may include:

- Thorough explanation of the study interview schedule and procedural requirements during the informed consent process.
- Collection of email and/or phone contact information at the study Baseline Screening and Enrollment interview.
- Repeated contact attempts to schedule appointments.
- Immediate follow-up for missed appointments.
- In-person approach of patients visiting the site for prenatal care if contact cannot be reestablished through email or phone.
- Follow-up with patients delivering at outside institutions to obtain verbal report of the delivery outcome and consent for release of medical records.

3.4. Participant Withdrawal

Regardless of the participant retention methods used, participants may voluntarily withdraw from the study for any reason at any time. The site PI also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants may also be withdrawn if the study sponsor, regulatory authorities, or site IRB terminate the study prior to its planned end date.

The study team will evaluate participants withdrawn from the study on a case-by-case basis to determine whether delivery outcomes may be collected from the chart and retained in analyses. A final determination will be made according to a participant's stated preference for use of her chart data and the data use guidelines set forth in the informed consent form.

4.0 STUDY ARMS

4.1. Standard of Care

Standard of care varies across study sites. Following is a description of the procedures in place at each site:

San Francisco Bay Area, California

<u>University of California San Francisco (UCSF)</u>

Women who establish prenatal care at UCSF are typically seen between 8 and 12 weeks gestation for their first obstetrical visit. The initial intake visit is in person and is conducted by various obstetric providers including nurse practitioners (NP), certified nurse midwives (CNM),

generalist obstetricians or maternal fetal medicine (MFM) specialists depending on patient preference or risk based upon questionnaire by the OB scheduling team.

A complete medical, surgical and obstetrical history and physical exam, including a viability/dating ultrasound, is performed. Note is made of prior pregnancy histories, including gestational age at delivery, pregnancy complications and modes of prior deliveries. If a patient gives a history of cesarean delivery (CD), attempts are made to obtain the operative report to review indications and hysterotomy type. Discussions regarding candidacy for trial of labor are initiated by all levels and type of OB care providers at the first OB visit and revisited in subsequent visits with discussions regarding risks/benefits and alternatives. Calculation and discussion of likelihood of successful vaginal birth after CS using the MFMU calculator is common but not universal. The discussions and patient choice are documented in the problem list. If the patient was followed by a NP or CNM throughout the pregnancy she is referred at least once to an obstetrician or MFM for a discussion regarding the mode of delivery. At 34-35 weeks gestation, if patient chooses ERCD, she is scheduled in the birth center OR schedule at 39 weeks. If she chooses to undergo TOLAC, a discussion of timing of delivery or induction of labor is conducted in the OB clinic with the clinician; otherwise spontaneous labor is awaited. Patients who choose to undergo a TOLAC do not sign written consents at UCSF. Surgical consents are signed by the inpatient OB team with the patient prior to ERCD.

Marin Community Clinic. At Marin Community Clinics, obstetric patients initiate care with an RN whose scope of practice includes intake examinations, patient triage, and initial review of laboratory and diagnostic results. At the intake appointment, the obstetric nurse reviews the patient's medical and obstetric history, initiates routine initial laboratory studies, and provides the patient with educational material. Most of the patients seen at our site, which is a Federally Qualified Health Care Center, are eligible for Medi-Cal, so the obstetric nurse also ensures that the patient begins the insurance eligibility process. After this initial intake appointment, patients are referred for an initial appointment with an obstetric provider who might be a nurse midwife, a family practice physician, or a nurse practitioner. Patients with complicated medical issues are referred to the two obstetricians who serve as consultants to the other providers.

Patients with a prior cesarean section are screened for PROCEED eligibility and participation in the study is discussed by the obstetric nurse at the initial intake appointment. Patients are also identified and screened during their subsequent visits with obstetric providers. The Site Principal Investigator is informed when a patient would like to participate and forwards demographic information for these patients to the PROCEED Study Coordinator who contacts the patients for interviews.

All patients who have had a prior cesarean and are eligible for a TOLAC are counseled regarding mode of delivery for their current pregnancy. A significant number of our patients are Spanish speaking and are scheduled between 24 and 34 weeks for a monthly group class in Spanish on the risks and benefits of TOLAC versus elective repeat cesarean section. The class consists of a group session followed by individual appointments with an obstetrician to address patient concerns and preference for mode of delivery. Patient who are English-speaking or speak another language are scheduled for an individual consultation with an obstetrician. Patients who elect trial of labor after cesarean are seen again to review their delivery plan if they have not yet delivered after 39 weeks. Patients who elect repeat cesarean are scheduled for an obstetric visit at 36 weeks to schedule a repeat cesarean section at 39 weeks.

Chicago, Illinois

Northwestern University Medical Center. Women who establish prenatal care at ambulatory practices associated with Northwestern Memorial Hospital are most often seen in the first trimester for a first obstetrical visit. An initial intake is conducted at which medical, surgical and obstetric histories are taken. Most obstetric providers are physicians, although there are groups with midwives as well, and in those groups patients who are eligible for care with either type of provider largely self-select into physician vs. certified nurse midwifery care. Providers review operative reports for prior cesareans if available. Discussions about delivery approach typically begin on the first prenatal visit and may be revisited throughout the course of the pregnancy. If elective repeat cesarean delivery (ERCD) is preferred, or even considered, a slot on the OR schedule is often reserved, at whatever gestational age and date are deemed acceptable and appropriate after conversations between the patient and provider.

Boston, Massachusetts

Massachusetts General Hospital. Women who establish prenatal care at Massachusetts General Hospital are typically seen between 8 and 12 weeks for a first obstetrical visit. An initial intake is conducted by a practice nurse at most sites, and often by phone at the largest site. During the initial intake, medical, surgical and obstetric histories are collected for new patients and are updated for returning patients. Prior pregnancy history is noted, including gestational age, pregnancy complications and modes of prior deliveries. Patients largely self-select into physician vs. certified nurse midwifery care, though access to physician care may be somewhat restricted to those with medical or obstetrical complexities at the three community health centers where prenatal care is provided. Operative reports for prior cesareans are reviewed for hysterotomy type, with findings documented in the problem list in the electronic medical record; attempts are made to obtain outside records for surgeries not performed at MGH or within the Partners Healthcare system. Discussions about approach of delivery generally begin as early as at the first prenatal visit and are revisited throughout the course of the pregnancy. Risks and benefits of trials of labor after cesarean are reviewed in detail and women's preferences, even if provisional, are recorded in their problem lists. Calculation and documentation of the likelihood of successful vaginal birth after cesarean using the "MFMU calculator" is common but not universal. If elective repeat cesarean delivery (ERCD) is preferred, or even considered, a slot on the OR schedule is often reserved, at whatever gestational age and date are deemed acceptable and appropriate after conversations between the patient and provider. The primary provider will often schedule a time when s/he is available. For patients desiring ERCD who are enrolled in midwifery care, a visit with a physician provider is often scheduled prior to the planned delivery date. For women considering TOLAC, risks and benefits of induction of labor are reviewed should indication (including post-term pregnancy) arise. In the third trimester, women sign written informed consent for care on Labor and Delivery, including for repeat cesarean delivery or TOLAC where applicable.

Note: At all study sites, usual care for women with a prior cesarean includes counseling by the provider regarding mode of delivery. No formal educational intervention, web tools, or decision support is in place at any site. Use of the NICHD VBAC prediction tool is at the discretion of the prenatal provider.

4.2. Intervention

The Prior Cesarean Decision app (Appendices 1 and 2) includes the following features: 1) approximately 15 minutes of web-based content, 2) topic-specific content and graphics, 3) user-specific risk data presented in a dynamic and interactive environment, and 4) content in both

English and Spanish. The program is organized into segments and sub-segments that are interactive and sequenced. To create a satisfying user experience and enhance user interaction, some segments include "learn more" buttons to access additional content. Users enter clinical information and responses to values clarification exercises, taking advantage of the mHealth platform to increase patient engagement while targeting both intuition and deliberation to optimize the effectiveness of decision support.[29]

The app was developed using a process based on the International Patient Decision Aids Standards Collaboration (IPDAS) quality checklist[30] to confirm that the content, development process, and effectiveness of the Prior Cesarean Decision app conform to the highest standards. Published data, as well as our own testing of prior interactive multimedia decision tools, provided the foundation for the content and framework for the Prior Cesarean Decision app.

Focus groups and one-on-one interviews were conducted at all sites prior to initiation of enrollment for the RCT. Women of varying literacy levels who were patients of the institution and had a prior cesarean section within the past three years were invited to participate in a one-time 60-90 minute feedback session with study personnel in which they completed a basic demographics questionnaire and were shown various versions of the app during the development process. The sessions were audio recorded and staff took notes of specific feedback to incorporate into the app. The app developers also attended some sessions to hear directly from potential future users. Participants were remunerated $60 for their participation.

5.0 STUDY PROCEDURES

5.1. Overview

The RC will perform a preliminary eligibility screening by chart audit of all women seeking prenatal services at the site (see section 5.1.1.). Women with one prior cesarean who speak English or Spanish and do not appear to have any contraindications to VBAC will be identified and approached for in-person eligibility review.

Women will be approached in the clinic waiting area before a prenatal appointment, informed of their potential eligibility for the study, and asked to complete and return a printed copy of the opt-in form (see section 5.1.2,). If time permits and the woman is eligible and interested in participating, screening, enrollment, and randomization will take place same-day and immediately after the opt-in form is completed.

All study instruments will be administered in the language preferred by the participant, English or Spanish. A baseline screening form will be completed to verify the woman's eligibility, then written informed consent obtained from those eligible and interested in participating. Participant sociodemographic characteristics, expected due date, and current preference as to delivery approach will be collected using a baseline questionnaire. The participant will then be randomized to app (intervention) or no app (control). Participants randomized to app will be provided an iPad tablet pre-loaded with the app to view at their own pace (see sections 4.2 and 5.1.3. for more information). A short health literacy assessment will be administered after the app. Apart from the app, the intervention arm will receive usual care. A woman randomized to no app will complete the baseline questionnaire including the health literacy assessment, and will not view the app.

Patient-reported secondary outcomes will be assessed at 34 weeks 0 days to 37 weeks 6 days gestation through a phone follow-up interview administered by an interviewer blinded to the

randomization group of the participant (see section 5.1.4.). After delivery, chart review will be performed by a blinded co-investigator to ascertain the primary outcome of delivery approach (TOLAC or ERCD), the secondary outcome of delivery mode (vaginal or cesarean) and any contraindications to TOLAC that developed post-randomization (see section 5.1.5.). Research assistants will also review the chart to collect other clinical data from the delivery encounter including the secondary maternal and neonatal morbidity outcomes.

Participants will receive $40 in remuneration for participating in the baseline screening and enrollment interview and $40 for participating in the phone follow-up interview. Participants who deliver at an outside institution will be contacted by telephone to collect self-reported delivery outcome and other pregnancy and delivery information as well as permission for release of the medical record (see section 5.1.6.).

5.1.1. Chart audit (<25 weeks gestation)

The medical charts of women who will be <25 weeks gestation at the next prenatal visit to the site will be reviewed for eligibility by a RC or provider at the site. Women with one prior cesarean who speak English or Spanish and have no contraindications to VBAC will be flagged for further in-person eligibility review.

5.1.2. Opt-in form (<25 weeks gestation)

Women flagged for follow-up according to the chart audit will be approached in the clinic waiting area before the prenatal appointment or told about the study by the provider during an OB visit. Women interested in participating will be asked to complete and return a printed copy of the opt-in form (Appendices 3 and 4). If the woman meets gestational age criteria for baseline screening (see section 5.1.3) and has enough time to complete the baseline screening and enrollment interview (approximately 15 minutes), the screening questionnaire can be administered on the same day (see section 5.1.3.). Otherwise, she will be contacted by the RC to schedule the screening in conjunction with an upcoming prenatal visit. A record of every woman approached will be kept in a REDCap database.

5.1.3. Baseline screening and enrollment interview (12 weeks 0 days to 24 weeks 6 days gestation)

Screening Questionnaire. In-person screening for eligibility will be administered by tablet when the woman is between 12 weeks 0 days and 24 weeks 6 days gestation, usually immediately after the opt-in form is collected. Eligibility will be assessed using a seven-question screening questionnaire (Appendices 5 and 6). A woman will be confirmed eligible if she self-reports all of the following: (1) a due date corresponding to a gestational age of 12 weeks 0 days to 24 weeks 6 days at time of interview, (2) carrying a singleton pregnancy, (3) a single prior cesarean section, (4) a cesarean section at her most recent delivery, (5) the cesarean section was not 'classical', i.e., the cut on the uterus does not run up and down, (6) does not recall any other uterine surgeries that would make her ineligible for a cesarean section, e.g. a myomectomy for removal of uterine fibroids, (7) planning to deliver at the current institution. Responses to the screening questionnaire will be collected in a REDCap database.

Consent. After the screening, printed informed consent and permission for release of medical records will be obtained from eligible participants using the consent and HIPAA forms (Appendices 7-10; see sections 8.2 and 8.3 for more information).

Baseline Questionnaire. The baseline questionnaire (Appendices 11 and 12) will be administered by tablet after consent. This form collects participant age, race/ethnicity, education, income, form of health insurance, estimated due date, and current preference for delivery approach. A

print copy of the questionnaire will be offered to the participant to follow along as questions are read aloud (Appendix 13). The RC will keep track of the time at the start and end of the interview and note if there is an interruption to the interview lasting more than 5 minutes. The RC will also record if anyone is with the participant during the interview. Questionnaire data will be collected in a REDCap database.

Randomization and intervention. Treatment group will be assigned according to a randomization table in REDCap generated by the statistician co-investigator. If randomized to app, the participant will be given a tablet to view the app at her own pace (Appendices 1 and 2). The app will provide information on potential maternal and neonatal complications from vaginal and cesarean deliveries, values clarification questions, and an individualized estimate of the likelihood of a successful TOLAC. After viewing the app, a printed summary sheet with her answers to the values clarification questions and probability of successful TOLAC will be provided to each participant to take home (Appendices 14 and 15). More information about the app is provided in section 4.2. A participant randomized to the control arm will not view the app. If she inquires about the intervention, she will be told it consists of standardized information about the benefits and risks of trial of labor and elective cesarean.

Health Literacy Assessment. The interview will conclude with a short health literacy assessment (Appendices 11 and 12) which evaluates a woman's ability to interpret a nutritional label. The assessment will be completed by both treatment arms.

Remuneration and follow-up reminder. Women who complete the baseline interview will receive $40 in remuneration in the form of a gift card (Appendices 16 and 17) or check.

5.1.4. Phone follow-up interview (34- to 37 weeks gestation)

The Phone Follow-up interview will be completed with participants in both arms of the study between 34- and 37 weeks 6 days gestation. The goal of this interview is to collect data on the secondary study endpoints of knowledge about TOLAC and ERCD; decisional conflict; shared decision-making regarding delivery approach; decision self-efficacy; and decisional satisfaction.

Chart audit. Before contacting a participant, the RC will review her chart to establish whether she is still pregnant, has already delivered, or has experienced pregnancy loss before 22 weeks.

Phone interview. If the participant has not yet delivered, she will be contacted by the RC at 33 weeks gestation to schedule a time for the phone follow-up interview. A copy of the phone follow-up questionnaire (Appendices 18 and 19) will be offered to the participant by email or mail so she may follow along as questions are read aloud. The questionnaire will be administered by a different interviewer and collected in a separate REDCap database than the baseline questionnaire to ensure the interviewer remains blinded to the participant's randomization assignment.

The phone follow-up interview will consist of: (1) a six-item short form of the Spielberger State-Trait Anxiety Inventory, which assesses the woman's general anxiety level[31], (2) eight questions to assess the woman's knowledge of TOLAC and ERCD adapted from a published questionnaire [32], (3) a 16-item Decisional Conflict Scale[33], (4) an 11-item Decisional Self-Efficacy scale[34], (5) a single-item assessment of the woman's preferred role in the decision-making concerning her delivery approach[35], (5) a 9-item shared decision making questionnaire (adapted from the SDM-Q-9[36]), and (6) a six-item Satisfaction with Decision Scale[37]. More information about these survey instruments can be found in section 7.1.2.

During the phone follow-up interview, the woman will be asked where she plans to deliver. If at an outside institution, the RC will request the participant's consent to be contacted again for the post-delivery questionnaire and to have a copy of her delivery record forwarded to the study team (see section 5.1.6.).

If the participant is no longer pregnant at the time of the phone follow-up interview, the RC will administer an abbreviated form of the phone follow-up questionnaire documenting where the woman delivered, date of delivery, delivery approach, and method of delivery. Women who had a loss before 22 weeks will not be contacted for a phone follow-up interview.

Remuneration. Women who complete the telephone interview will receive $40 in remuneration in the form of a gift card or check.

5.1.5. Chart audits (after delivery)

Participant charts will be reviewed after delivery to abstract delivery approach, delivery mode, and other clinical data (Appendices 20 and 21). Abstraction of delivery outcome data and any contraindications to TOLAC before delivery will be performed by a PI, co-investigator or research coordinator who is blinded to the randomization assignment. Other data from the delivery encounter, including maternal and neonatal morbidities and findings from the cervical exam at time of admission, will be abstracted by the RC. Data will be collected in REDCap. A comments box on the data collection form will allow RCs to document challenges interpreting the chart, which can also be raised at a coordinator call or addressed to a co-investigator or PI if necessary.

Investigator review. For investigator review of outcomes, the delivery note may provide clarity; in other cases, review of both the labor and delivery and prenatal record will be necessary. Whether the patient developed an absolute contraindication to TOLAC before her delivery admission may be obtained from the op note. Breech, Previa, or any congenital anomaly not compatible with vaginal delivery should be documented. To establish planned approach for the current delivery, the investigator will use the following definitions:

- Participant planned ERCD if:
    - Delivered by scheduled ERCD at 39 weeks prior to labor for no reason other than desired RCD rather than TOLAC
    - Presented in labor prior to scheduled cesarean, and opted to proceed with cesarean for primary reason that desired RCD rather than TOLAC
    - Presented with indication for delivery prior to scheduled cesarean (preeclampsia, IUGR, NRFT) and opted to proceed with cesarean for primary reason that desired RCD rather than TOLAC

      Note: If there are two indications for RCD in the chart, including a nonelective indication for timing of delivery less than 39 weeks, the investigator will code the first as the "nonelective" indication and the second as ERCD.

- Participant considered TOLAC if:
    - Underwent TOLAC
    - Planned TOLAC if labor prior to certain gestational age, but reached that gestational age limit and underwent ERCD
    - Planned TOLAC if spontaneous labor, but then developed an indication for induction and underwent ERCD

5.1.6. Post-delivery phone interview for outside deliveries (after due date)

If a participant's due date has elapsed by more than three weeks and there is no record of the delivery at the site, she has likely delivered at an outside institution. In such cases, the RC will contact the participant by phone or email to set up a time for the post-delivery phone interview. During the interview, the participant will be queried for self-report of the date of delivery, delivery approach and mode, and other pertinent information such as whether the outside facility offers TOLAC, whether the woman experienced contractions or rupture of membranes, use of pitocin for labor augmentation, use of forceps or vacuum to assist with delivery, baby's birthweight, maternal weight gain during pregnancy, and other information. In addition, the RC will request the name of the outside institution where the woman delivered and her permission to contact the institution for release of her delivery record. Responses will be collected using the post-delivery questionnaire (Appendices 22 and 23) and stored in a REDCap database (Appendix 24).

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1. Safety Monitoring and Clinical Data Review

A multi-tiered safety review process will be followed for the duration of this study. Close cooperation between the principal investigator, site principal investigators and other co-investigators, project manager, study coordinators, study statistician, and other study team members will be necessary to monitor participant safety and to respond to concerns in a timely manner. The investigative team will have monthly conference calls during the period of study implementation and additional ad hoc calls will be convened as needed.

RCs will report all participant complaints to the investigative team. These will be discussed during weekly/biweekly RC calls and monthly investigator calls.

Each study site is responsible for continuous close monitoring and management of adverse events (AE) in accordance with the protocol for AE reporting at their home institution (Appendices 27-30). The study site PIs are responsible for the initial evaluation and reporting of safety information and for alerting the investigative team if unexpected concerns arise.

6.2. Reporting Requirements for this Study

The site PI or RC will report an adverse event to the local IRB if study staff determines it may qualify as an Unanticipated Problem or Adverse Event because the event meets all three criteria listed below:

- Unanticipated in severity or frequency AND
- At least *possibly* related to the study intervention AND
- Is Serious OR not serious but suggests placing subjects or others at greater risk

In addition, all SAEs will be reported to the study team within 72 hours of recognition by study staff.

7.0 STATISTICAL CONSIDERATIONS

7.1. Endpoints

7.1.1. Primary Endpoint

Consistent with the primary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will be more likely to undergo TOLAC compared to women who receive only usual care, the following endpoint will be assessed in the medical record for the delivery:

- Proportion of women who elect TOLAC

7.1.2. Secondary Endpoints

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will be more likely to have a VBAC compared to women who receive only usual care, the following endpoint will be assessed in the medical record for the delivery:

- Proportion of women who have a VBAC

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will be more knowledgeable about TOLAC and ERCD and their potential outcomes compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Knowledge about TOLAC and ERCD and their potential outcomes, as assessed with a modified version of a published questionnaire.[32]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will experience less decisional conflict compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Decisional conflict regarding delivery approach, as measured based on the participant's score on a well-validated Decisional Conflict Scale[33] recommended for the assessment of decision quality by the IPDAS.[38] This measure generates an overall conflict score and 5 subscale scores and has been used extensively to evaluate patient-centered decision tools in a wide range of clinical contexts.[39]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will report higher levels of shared decision making regarding delivery approach compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Shared decision making, as measured using the SDM-Q-9, a psychometrically evaluated self-assessment tool.[36]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will experience greater decision self-efficacy compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Decision self-efficacy, as measured using a validated 11-item Decisional Self-efficacy Scale.[34]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will report higher levels of decision satisfaction compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Decisional satisfaction, as measured using the Satisfaction with Decision Scale, a 6-item scale designed to measure global satisfaction with a decision and to differentiate this from related aspects of satisfaction.[37]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will experience lower rates of maternal and neonatal morbidity

compared to women who receive only usual care, the following endpoints will be assessed in the medical record for the delivery:

- Maternal major morbidity, defined as any of: uterine rupture, hysterectomy, surgical injury (bowel, bladder/ureter, or other), maternal death.
- Maternal minor morbidity, defined as any of: blood transfusion, postpartum febrile morbidity (endometritis, cellulitis, urinary tract infection, or other infection)
- 3rd or 4th degree lacerations
- Neonatal death or HIE, defined as any of: stillbirth/fetal demise (antepartum or intrapartum), neonatal death, HIE
- Neonatal respiratory morbidity, defined as any of: respiratory morbidity requiring CPAP or intubation
- Neonatal intensive care unit (NICU) admission

7.2. Sample Size

Table 1 shows the minimum difference in TOLAC due to the Prior Cesarean Decision app that has 80% power. For a recruitment goal of 1,320 participants (1:1 per intervention arm) and assuming 5% loss to follow-up and a baseline rate of 33% in the control group, we will have at least 80% power to detect an 8% absolute increase in TOLAC due to the app.

Table 1: Minimum detectable effects for randomization α=.05, two-sided, power = 80%. LTFU = lost to follow-up rate.

Outcome	Assumptions	Effect Measure	N=1,200	**N=1,320**	N=1,440	N=1,660
TOLAC	Baseline rate (33%) LTFU (5%)	Absolute increase (%)	8%	**8%**	7%	7%

7.3. Blinding

Assessors of the primary and secondary outcomes will remain blinded to the randomization assignment throughout the study. The study participant and the RC who administers the baseline screening and enrollment interview will be aware of the participant's randomization assignment. Phone follow-up questionnaires and chart audits will be administered by a different interviewer and collected in a separate database than the baseline questionnaire to ensure the interviewer remains blinded to the participant's randomization assignment during collection of study endpoints.

7.4. Data Analysis

We will present sample characteristics by treatment assignment in the form of n's and %'s for categorical variables and means/standard deviations or medians and interquartile ranges for continuous variables.

For our primary outcome TOLAC and major secondary outcome VBAC, we will calculate the proportion with the outcome by treatment arm and test for differences between treatment arms using a Poisson regression model which has been adjusted for recruitment site and

language of interview and includes robust standard errors. Comparisons will be presented in the form of relative risks and 95% confidence intervals. Differences between treatment arms for the maternal and neonatal morbidity outcomes will be evaluated in the same manner. For continuous outcomes (e.g., decisional conflict, shared decision making regarding delivery approach, decision self-efficacy, and decisional satisfaction), we will calculate the mean score by treatment arm and test for differences using linear regression models adjusted for recruitment site and language of interview.

For our primary outcome TOLAC and major secondary outcome VBAC, we will examine interactions of treatment arm by the a priori defined factors of site, race/ethnicity, and language. For each interaction, differences will be evaluated using a Poisson regression model with an interaction term for treatment arm by subgroup.

Analyses will exclude women who had a pregnancy loss before 22 weeks gestation. We will also perform a sensitivity analysis of TOLAC and VBAC rates and differences in TOLAC and VBAC between treatment arms after excluding women who develop placenta previa or breech presentation.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1. Ethical Review

Informed consent forms will pass through review and approval by the local IRB. as will participant education and recruitment materials, any other documents requested by the IRB, and any subsequent modifications to a document after approval. Review will be with respect to scientific content and compliance with applicable research and human subjects regulations.

IRB review of the study protocol will occur at least annually. The Site PI or RC will provide safety and progress reports to the IRBs at least annually and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

8.2. Informed Consent

Written informed consent will be obtained from each study participant prior to enrollment using an informed consent form approved by the local IRB in accordance with all applicable regulations. A copy of her signed informed consent form will be offered to the participant (Appendices 7 and 8).

8.3. HIPAA

Permission for release of medical records for ascertainment of clinical endpoints will be obtained from participants with the Health Insurance Portability and Accountability (HIPAA) form, which documents the personal health information that may be released, to whom it may be released, how it may be used, when permission for its release expires, and under what terms permission may be cancelled (Appendices 9 and 10).

8.4. Risks

Breach of confidentiality. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others. We are evaluating a mobile health intervention linked to a cloud platform and there is the possibility that study participation could become known to others despite the use of firewalls, password protection, and other security measures.

8.5. Benefits

Participation in the intervention arm of this study may lead to improved rates of TOLAC and other beneficial outcomes as posited in sections 2.1 and 2.1 of this manual. There may be no direct benefits to participants in the control arm of this study; however, they and others may benefit in the future from information learned from this study.

8.6. Incentives

Participants will be compensated for their time and effort in this study through remuneration of $40 following participation in the baseline interview and $40 following participation in the phone follow-up questionnaire. Remuneration will be the in the form of a gift card (Appendices 16 and 17) or check.

8.7. Confidentiality

All study-related information will be stored securely at the study site in locked file cabinets or on password-protected databases managed in accordance with section 9.1.3. of this study protocol. Participant study information will not be released without the written permission of the participant except as necessary for monitoring by the NIH and/or the site IRB.

9.0 ADMINISTRATIVE PROCEDURES

9.1. Study Coordination

Study implementation will be directed by this study protocol. Study case report forms and other study instruments are attached as Appendices 1-30. Protocols for training and study team communication are covered in sections 9.1.1. and 9.1.2. Section 9.1.3 reviews database management and data quality monitoring plans. Use of information is described in Section 9.1.4.

9.1.1. Trainings

The project manager at UCSF will train the RCs and other project staff at each of the sites. Topics covered will include:

- Study background, justification & aims
- Inclusion & exclusion criteria, eligibility screening
- Participant tracking in REDCap
- Appointment scheduling
- Approaching potentially eligible participants
    - Etiquette for in-person approach in the clinic waiting bay
    - Opt-in/opt-out forms
- Informed consent
- Randomization protocol
- Questionnaires
    - Baseline face-to-face questionnaire
    - Phone follow-up questionnaire
- Equipment
    - iPads
    - Portable Wi-Fi-enabled color printers

- Chart review
- Remuneration

9.1.2. Study Communication

Calls and in-person meetings will be scheduled throughout the study period to ensure clear communication, collegial collaboration, and rapid response to any challenges that may arise.

Investigator Calls.

The PI will lead monthly conference calls with the site PIs, co-investigators, project manager, and data manager. Topics to be discussed will include:

- Project timelines
- Recruitment plans
- Enrollment and retention reports
- Study design and implementation
- Questionnaire revisions (as necessary)
- Data analysis plans, progress and results
- Manuscript and abstract plans and progress
- Review of draft manuscripts and abstracts
- IRB renewals and modifications
- Budgets and contracts
- Other study management issues as needed

Research Coordinator Calls.

The project manager at UCSF will hold weekly 30-minute phone calls with the research coordinators for the first six months of the project. After six months, they will switch to a bi-weekly conference call schedule. The PI or a site PI will participate as needed. Coordinator calls will cover the following topics:

- Current totals interested, scheduled for enrollment, enrolled, scheduled for phone follow-up, followed-up, charts reviewed, by site
- Successes, challenges, and new ideas for:
    - Screening and approaching patients
    - Reaching recruitment targets
    - Utilizing technology (iPads, printers, Wi-Fi)
    - Administering questionnaires
    - Interfacing with the app
    - Scheduling and coordinating follow-up interviews and chart reviews
    - Carrying out follow-up interviews and chart reviews
    - IRB modifications
    - Other issues as needed

Annual Meetings.

Each year, the PI will host an annual in-person meeting of one- to two days with the site PIs, co-investigators, project manager, data manager, and RCs. Topics covered will be similar to the monthly calls but with time for lengthier discussion. Parallel break-out sessions for investigators and staff may be held to cover topics relevant to each group. A meeting of the PI and site PIs may also take place to discuss confidential matters and critical leadership/management decisions. A second annual meeting for broader visioning of scientific goals and dissemination plans will be held in-person among study members attending the annual Society for Maternal Fetal Medicine conference.

9.1.3. Database Management and Data Quality Monitoring

Randomization assignment, survey responses, and chart audit data for all sites will be collected and stored in REDCap databases hosted centrally at UCSF. Data will be behind an institutional firewall and accessible through a web portal via login credentials known only to qualified study staff. Randomization assignment will be collected in a separate database than the phone follow-up questionnaire and chart audits to ensure staff remain blinded to treatment group while gathering outcome data. Sites will maintain their own tracking and recruitment logs in local REDCap databases (Appendix 24). Protected health information, such as patient names, medical record number, estimated due date, clinic visit schedule, telephone number and email address will be collected on the tracking and recruitment log to aid with scheduling and participant follow-up. A unique study identifier will be generated for each participant to link records across databases.

Data from the app will be collected through a secure, password-protected online portal linked to a PostGRE SQL database on a Heroku cloud platform, which provides best-in-class server security, including firewalls, physical security, and regular compliance auditing.

Clinical, survey and app data will be transferred to SAS statistical software for cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the study sites on a routine schedule for verification and resolution.

9.2. Use of Information and Publications

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. Presentation and publication of the results of this study will be governed by guidelines determined by the study team and as necessary and appropriate by their associated institutions policies. Any presentation, abstract, or manuscript will be approved by the protocol chair prior to submission.

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11.0 APPENDICES

Appendix	Name of Document	Version Date
1	App PDF-English	112015
2	App PDF-Spanish	112015
3	Opt-in form-English	111615
4	Opt-in form-Spanish	112015
5	Screening questions-English	111615
6	Screening questions-Spanish	112015
7	UCSF Consent-English	111615
8	UCSF Consent-Spanish	112015
9	UCSF HIPAA-English	111615
10	UCSF HIPAA-Spanish	112015
11	Baseline Questionnaire-English	111615
12	Baseline Questionnaire-Spanish	112015
14	App summary sheet-English	111615
15	App summary sheet-Spanish	112015
16	UCSF Gift Card Receipt-English	111615
17	UCSF Gift Card Receipt-Spanish	112015
18	Phone Follow-up Questionnaire-English	111615
19	Phone Follow-up Questionnaire-Spanish	112015
20	Chart Review tool (investigator)	111615
21	Chart Review tool (RC)	111615
22	Post Delivery Phone Questionnaire for Outside Deliveries-English	111615
23	Post Delivery Phone Questionnaire for Outside Deliveries-Spanish	112015
24	RedCap tracking & recruitment log data dictionary	010416
25	IRB/CHR Approval Letter-UCSF	121415
26	IRB Approval Letter-Massachusetts General	121815
27	IRB Approval Letter-Northwestern	121015
28	IRB Adverse Event Reporting-Northwestern	111315
29	IRB Adverse Event Reporting-Mass. General	111315
30	IRB Adverse Event Reporting-UCSF	111315

Note: The only protocol change we instituted on this protocol was the addition of a site in San Francisco (California Pacific Medical Center, St. Luke's Campus). Because of this addition, we added new study team members to the protocol and we included a description of usual care at that site. No changes were made to the statistical analysis plan.

Effect of a Patient-Centered Decision App on TOLAC: An RCT

The PRiOr CEsarEan Decision App (PROCEED) Study

Sponsored by:
US National Institute of Health
Grant #1R01HD078748

IRB Approvals
UCSF/Marin Community Clinic: CHR #13-11707
Massachusetts General Hospital: IRB #2015P002284
Northwestern University Medical Center: IRB #STU00104496
St. Luke's Campus, California Pacific Medical Center: IRB #2017.096EXP

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Version Date: 28 September 2018
v2
The PRiOr CEsarEan Decision App (PROCEED) Study

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PERSONNEL AND DUTIES

Principal Investigator (PI)

The PI is experienced in all aspects of the design, conduct and oversight of randomized controlled trials and prospective studies at multiple clinical sites and is an expert in the fields of medical decision-making, preference (utility) measurement, and decision-assisting tool creation and evaluation. The PI will take a lead role in all aspects of the proposed project, working with the site PIs, other co-investigators, and staff members to ensure timely and accurate completion of the project. The PI will direct day-to-day activities and provide overall governance and scientific leadership to the study.

Statistician Co-investigator

The statistician co-investigator will direct analysis strategy for study design and manuscript preparation. The statistician will also oversee data analysis by the analyst and advise the PI and other co-investigators on methodological issues.

Site Principal Investigator (site PIs)

The site PIs will meet monthly by phone and biannually in person (along with the other co-investigators) to contribute to the overall study design and ensure each site is executing the study as prescribed. Site PIs are responsible for hiring and training site staff and will provide clinical and research expertise in the design and implementation of study instruments and protocols. Site PIs will monitor study enrollment and troubleshoot any recruitment issues as needed. They will also assist with chart review for participant delivery outcomes.

Other Co-investigators

Additional co-investigators will join the monthly calls and biannual in-person meetings. They will support patient recruitment from the obstetric practices at each site and will provide clinical input into data analyses and manuscripts for submission to peer-reviewed journals. They will also assist with chart review for participant delivery outcomes.

Project Manager

The project manager is responsible for the overall operations of the study, including managing recruitment and enrollment, guiding IRB submissions, and scheduling and preparing agendas for investigator and coordinator meetings. The project manager will monitor project timelines and ensure recruitment goals are met and recruitment and data collection are carried out per established protocols. The project manager will document any revisions to protocols and surveys and acquire IRB approvals as needed. The project manager will also work with the data manager/statistical analyst to design and implement study databases.

Data Manager/Statistical Analyst

The data manager/statistical analyst is responsible for creating and managing all databases for the project, monitoring data quality, and conducting data cleaning and statistical analyses under the direction of the statistician co-investigator and PIs.

Research Coordinators/Interviewers

The Research Coordinators (RCs) are the primary administrative points of contact for the study. They will prepare and submit all materials for IRB approval including the initial application, renewals, and all modifications. They will pilot and fine-tune study instruments; screen, consent, and interview participants; randomize participants per protocol; abstract medical data from

charts; and distribute participant remuneration. They will be responsible for following the guidelines for study operations outlined in this protocol and will email the UCSF project manager in the event of any protocol violations (e.g., mis-randomization, erroneous inclusion of subjects in the study, breach of confidentiality). They will participate in weekly or biweekly conference calls with the project manager and one or more PIs to go over recruitment and data collection activities and targets.

STUDY SCHEMA

Purpose: To assess the effect of the PROCEED Prior Cesarean Decision Support app (versus usual care without the app) on rates of trial of labor after cesarean (TOLAC) among pregnant women with a prior cesarean delivery (CD).

Design: This is a two-armed randomized controlled trial (RCT) among 1,320 English- or Spanish-speaking pregnant women (1:1 randomization sequence for the intervention).

Study Population: Pregnant women receiving prenatal care at a participating healthcare facility. Women will be eligible to enroll if they meet all of the following criteria.

Inclusion criteria:

- Between 12 weeks 0 days and 24 weeks 6 days gestation at enrollment
- Speak English or Spanish
- Have had one and only one prior CD
- Prior low transverse cesarean

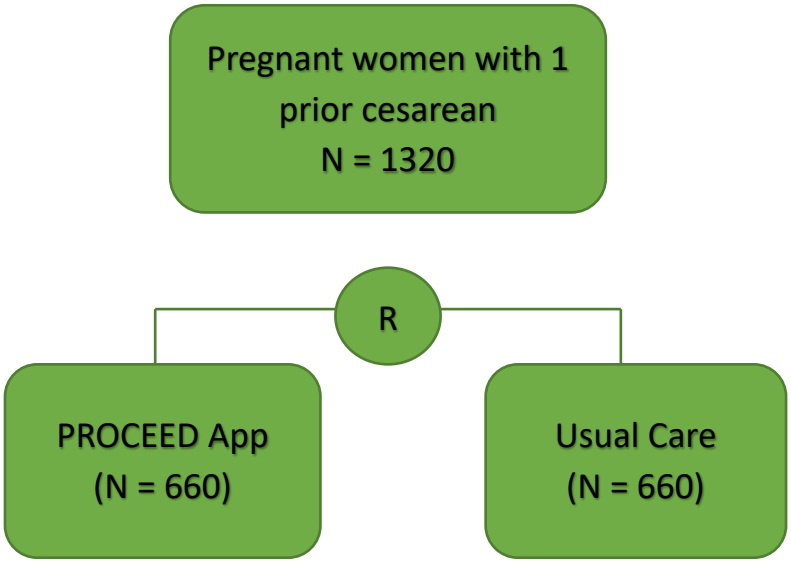
Exclusion criteria:

- No prior cesarean delivery, or more than one
- Multiple gestation pregnancy
- Prior vaginal birth after cesarean
- Any contraindications to TOLAC (prior classical cesarean, prior uterine surgery, T-incisions, other contraindication)
- Delivering at outside institution

Study Size: The recruitment goal is 1,320 participants, for a recruitment rate of 40 participants per month and a final subset of 627 per arm (1254) projecting 5% loss to follow up.

Study Intervention:	Participants in the intervention arm will be provided with the PROCEED Prior Cesarean Decision app, which includes approximately 15 minutes of dynamic web-based informational content including potential maternal and neonatal complications from vaginal and cesarean deliveries, values clarification questions, and individualized estimates of likelihood of successful TOLAC.
Study Duration:	Data collection start date: January 2016 Estimated data collection end date: July 2019
Primary Hypothesis:	Compared to women who receive usual care only, women who are randomized to use the Prior Cesarean Decision app will be more likely to undergo TOLAC.
Secondary Hypotheses:	Compared to women who receive usual care only, women randomized to use the Prior Cesarean Decision app will: 1. be more likely to have a vaginal birth after cesarean (major secondary outcome) 2. be more knowledgeable about TOLAC and elective repeat cesarean delivery (ERCD) and their potential outcomes 3. experience less decisional conflict 4. report higher levels of shared decision making regarding delivery approach 5. report higher levels of decision self-efficacy 6. report higher levels of decision satisfaction 7. experience lower rates of maternal and neonatal morbidities
Study Sites:	University of California, San Francisco Marin Community Clinic California Pacific Medical Center, St. Luke's Campus Massachusetts General Hospital Northwestern University Medical Center

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



12.0 INTRODUCTION

12.1. Background and Prior Research

Public health impact of cesarean rate in the US. Cesarean delivery (CD) is the most common inpatient surgery in the US, accounting for nearly one third of births annually. In the last decade, the CD rate has increased by approximately 50%, with almost 1.3 million procedures performed in 2012.[1] Moreover, at $7.8 billion annually, these deliveries account for almost half of childbirth-related expenses of hospitalization.[2] CDs have been associated with an increase in major maternal morbidity,[3–5] with corresponding increases in length of inpatient care following delivery and frequency of hospital readmission.[6] Organizations including Healthy People[7], the American College of Obstetricians and Gynecologists (ACOG)[8], and the American College of Nurse Midwives[9] have targeted reducing the CD rate as an important public health goal for more than a decade; however, identifying interventions to achieve this goal has proven challenging.

Causes and consequences of the rising rate of repeat cesareans. Repeat CDs are a significant contributor to the increased cesarean rate, resulting from the combination of a rising rate of primary CD and a decreasing rate of vaginal birth after cesarean, which declined from a high of 28.3% in 1996[2] to 9.2% in 2010.[10] Why the VBAC rate has decreased so dramatically remains a subject of debate. Numerous medical and nonmedical factors have been posited as contributing to this decline, including the decreasing number of hospitals willing to provide this option and the diminishing number of obstetric providers who offer this approach. In addition, a substantial portion of the decrease is related to women foregoing trial of labor after cesarean (TOLAC) even though their hospitals and obstetricians provide the opportunity. For example, among hospitals in the NICHD Maternal-Fetal Medicine Units network, TOLAC rates declined from 51.8% to 29.8% ($p<.001$) from 1999-2002, even though TOLAC continued to be offered at all sites.[11] In a study of "good TOLAC candidates" at a 14-hospital network where TOLAC was available, the average TOLAC rate was only 30%.[12] And at Northwestern, one of the clinical sites for our study,

TOLAC rates decreased by two-thirds from 1995 to 2010 although all providers offer this labor approach.

Importantly, the declining VBAC rate is *not* primarily due to new and more concerning information about the risks of TOLAC; recent epidemiologic studies have demonstrated that the core population-level outcomes of TOLAC, such as the chance of VBAC or of uterine rupture if a TOLAC is attempted, are no different today than they were three decades ago.[2,13–15] Similarly, this decline is not primarily due to changes in characteristics of the population that would make VBAC less likely if TOLAC is undertaken; these decreases in TOLAC have affected all women, regardless of their probability of VBAC or risks of adverse TOLAC outcomes.[11] The extent to which these changes are driven by patient preferences is not known. Data from qualitative studies offer some insight, but the value of that information is limited by the non-generalizability of the study populations and the lack of quantitative analyses.[16–21] Furthermore, while decreased TOLAC rates are occurring throughout the US, there are persistent, unexplained racial/ethnic, geographic, and socioeconomic differences in rates of TOLAC and VBAC.[22] This variation, in the absence of a demonstrated basis in clinical science or patient preferences, raises concern about the efficiency, effectiveness, and patient-centeredness of approach to delivery after CD.[23]

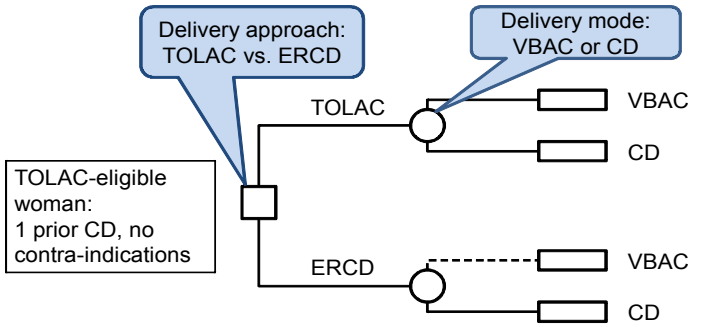


Figure 1. Delivery approach versus delivery mode. For women who are eligible for trial of labor after cesarean (TOLAC), a decision regarding the **delivery approach (**whether to schedule an **elective repeat cesarean delivery (ERCD)** or to undergo **TOLAC)** is made. The TOLAC rate is the percentage of eligible women who undergo a TOLAC (versus an ERCD). If TOLAC is chosen, the ultimate **delivery mode (VBAC or CD)** is uncertain. Most, but not all, women who plan an ERCD will deliver via CD.

Call to action. An NIH consensus conference statement noted that "the informed consent process for TOLAC and ERCD should be evidence-based, minimize bias, and incorporate a strong emphasis on the values and preferences of pregnant women," and recommended "interprofessional collaboration to refine, validate, and implement decision-making and risk assessment tools" to accomplish that goal.[22] Given the broad policy support for shared decision making in this context,[22,24] the large absolute number of women facing the choice of TOLAC, and the short- and long-term consequences of this decision for mothers and babies, an intervention aimed at informing patients and helping them articulate their preferences could lead to improvements in the decision making process and have a significant impact on the health of individuals and the health care system.[25,26] Our overarching goal is to create and evaluate a tool to help TOLAC-eligible women delivering at hospitals that offer TOLAC consider individualized risk assessments, incorporate their values and preferences, and participate in a shared decision making process with their providers to make informed decisions about delivery approach. We believe this improved informed decision making process will lead to increased TOLAC.

Our prior studies of decision making. In a recently completed randomized study (R01 HD049686), PI Kuppermann and colleagues found that women who used a prenatal testing decision tool had significantly lower uptake of invasive diagnostic testing, greater knowledge

about testing and birth defects, and better comprehension of the risks of amniocentesis or chorionic villus sampling.[27] We believe the PROCEED study also has the potential to generate an evidence-based intervention that may lower the overall CD rate among diverse populations of women, a critical yet elusive goal in obstetric care. Moreover, because the Prior Cesarean Decision app will make explicit the probability of achieving VBAC, it is expected that the group of women who undertake TOLAC after using the decision app will be enriched with those who are more likely to succeed in their attempt. As over 90% of morbidity occurs in women who undertake TOLAC but ultimately have a cesarean during labor[28], this app may also lower the rate of CD without increasing either maternal or perinatal morbidity.

13.0 STUDY HYPOTHESES AND DESIGN

13.1. Primary Hypothesis

The primary hypothesis of this study:

- Compared to women who receive usual care only, women who are randomized to use the Prior Cesarean Decision app will be more likely to undergo TOLAC.

13.2. Secondary Hypotheses

The secondary hypotheses of this study are:

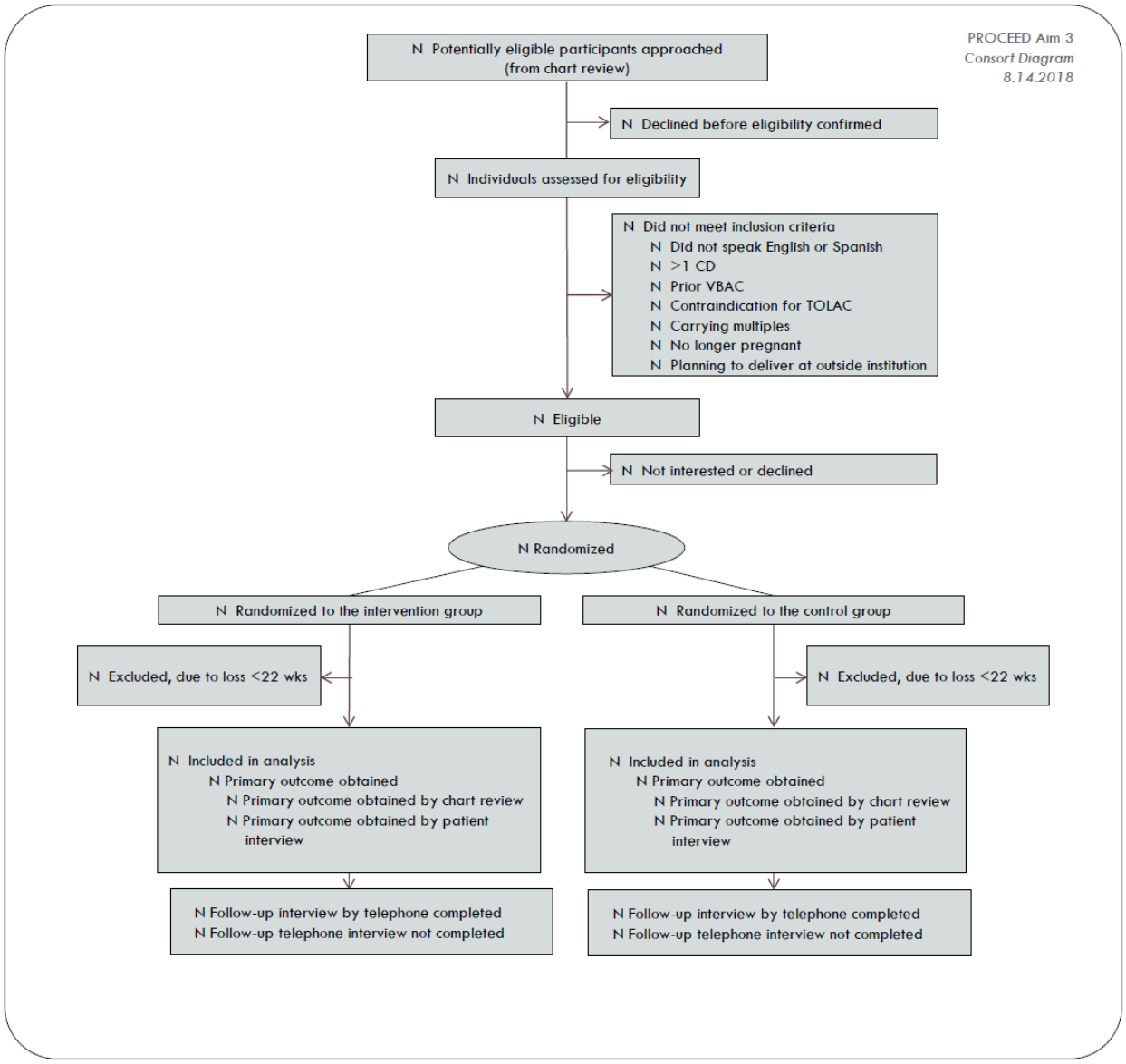
- Compared to women who receive usual care only, women randomized to use the Prior Cesarean Decision app will:

8. be more likely to have a vaginal birth after cesarean (VBAC) (major secondary outcome);
9. be more knowledgeable about TOLAC and ERCD and their potential outcomes;
10. experience less decisional conflict;
11. report higher levels of shared decision making regarding delivery approach;
12. report higher levels of decision self-efficacy;
13. report higher levels of decision satisfaction; and
14. experience lower rates of maternal and neonatal morbidities

13.3. Study Design

This is a two-armed RCT to assess the impact of a Prior Cesarean Decision app on the delivery outcomes of 1,320 English- or Spanish-speaking women with a prior cesarean delivery (1:1 randomization sequence for the intervention). Following is a consort diagram of the study:

Figure 2. Consort diagram



13.3.1. Timeline

Randomized controlled trial (n=1320)	2016				2017				2018				2019				2020	
	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Sep-Dec	Jan-Mar	Apr-Jun
Recruit RCT																		
Phone follow-up																		
Chart reviews																		
Create databases, enter and clean data																		
Analyze data and prepare manuscripts																		

13.3.2. Randomization

Randomization tables will be generated with SAS v9.4 using the RAND function utilizing the Mersenne-Twister random number generator. To make treatment assignments difficult to anticipate, the program will generate randomly permuted blocks of 8, 10, and 12 in random order. Randomization will be stratified by language (English/Spanish) and recruitment site. Randomization tables will be uploaded into a randomization module in the study database by the data analyst. To protect the integrity of the randomization sequence, RCs will not have access to the randomization tables.

14.0 STUDY POPULATION

A total of 1,320 pregnant women between 12 weeks 0 days and 24 weeks 6 days gestation with one prior cesarean will be enrolled into the study from three distinct geographic areas of the United States. Three sites serve primarily lower income women, with many Spanish speakers. The remaining three sites serve primarily English-speaking communities of higher socioeconomic status.

Participants will be randomized to receive the Prior Cesarean Decision app or usual care, stratified by site and language. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. They will be approached, screened, and enrolled as described in Sections 5.1.1., 5.1.2., and 5.1.3. Issues related to participant retention and withdrawal from the study are described in Sections 3.3 and 3.4, respectively.

14.1. Inclusion Criteria

Women who meet all of the following criteria are eligible for inclusion in the study:

- Prior cesarean delivery
- Between 12 weeks 0 days and 24 weeks 6 days gestation at enrollment
- English- or Spanish speaker
- Prior low transverse cesarean
- Unknown scar but TOLAC eligible

14.2. Exclusion Criteria

Women who meet any of the following criteria will be excluded from this study:

- No prior cesarean delivery, or more than one
- Multiple gestation pregnancy
- Unable to speak English or Spanish
- Prior VBAC
- Ineligible for TOLAC (due to prior classical cesarean, prior uterine surgery, T-incision, or other contraindication)
- Delivering at outside institution

14.3. Participant Retention

Once a participant enrolls in PROCEED, the study site will make every effort to retain her in the study for the entire follow-up period in order to minimize possible bias associated with loss to follow-up. Components of such procedures may include:

- Thorough explanation of the study interview schedule and procedural requirements during the informed consent process.
- Collection of email and/or phone contact information at the study Baseline Screening and Enrollment interview.
- Repeated contact attempts to schedule appointments.
- Immediate follow-up for missed appointments.
- In-person approach of patients visiting the site for prenatal care if contact cannot be reestablished through email or phone.
- Follow-up with patients delivering at outside institutions to obtain verbal report of the delivery outcome and consent for release of medical records.

14.4. Participant Withdrawal

Regardless of the participant retention methods used, participants may voluntarily withdraw from the study for any reason at any time. The site PI also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants may also be withdrawn if the study sponsor, regulatory authorities, or site IRB terminate the study prior to its planned end date.

The study team will evaluate participants withdrawn from the study on a case-by-case basis to determine whether delivery outcomes may be collected from the chart and retained in analyses. A final determination will be made according to a participant's stated preference for use of her chart data and the data use guidelines set forth in the informed consent form.

15.0 STUDY ARMS

15.1. Standard of Care

Standard of care varies across study sites. Following is a description of the procedures in place at each site:

San Francisco Bay Area, California

<u>University of California San Francisco (UCSF) and Zuckerberg San Francisco General Hospital (ZSFG)</u>

Women who establish prenatal care at UCSF are typically seen between 8 and 12 weeks gestation for their first obstetrical visit. The initial intake visit is in person and is conducted by

various obstetric providers including nurse practitioners (NP), certified nurse midwives (CNM), generalist obstetricians or maternal fetal medicine (MFM) specialists depending on patient preference or risk based upon questionnaire by the OB scheduling team.

A complete medical, surgical and obstetrical history and physical exam, including a viability/dating ultrasound, is performed. Note is made of prior pregnancy histories, including gestational age at delivery, pregnancy complications and modes of prior deliveries. If a patient gives a history of cesarean delivery (CD), attempts are made to obtain the operative report to review indications and hysterotomy type. Discussions regarding candidacy for trial of labor are initiated by all levels and type of OB care providers at the first OB visit and revisited in subsequent visits with discussions regarding risks/benefits and alternatives. Calculation and discussion of likelihood of successful vaginal birth after CS using the MFMU calculator is common but not universal. The discussions and patient choice are documented in the problem list. If the patient was followed by a NP or CNM throughout the pregnancy she is referred at least once to an obstetrician or MFM for a discussion regarding the mode of delivery. At 34-35 weeks gestation, if patient chooses ERCD, she is scheduled in the birth center OR schedule at 39 weeks. If she chooses to undergo TOLAC, a discussion of timing of delivery or induction of labor is conducted in the OB clinic with the clinician; otherwise spontaneous labor is awaited. Patients who choose to undergo a TOLAC do not sign written consents at UCSF. Surgical consents are signed by the inpatient OB team with the patient prior to ERCD.

California Pacific Medical Center, St. Luke's Campus. Pregnant women establish prenatal care typically in the first trimester with a midwife. The midwife collects a pregnancy history, including mode of delivery for any prior pregnancies. Subsequent prenatal care visits may be with an obstetrician or a midwife depending on patient's preferences and co-morbidities. Those who have had a prior cesarean meet with an obstetrician late in the second trimester or early third trimester to discuss delivery approach. Women who are eligible for TOLAC describe the circumstances of their previous cesarean to determine if the indication for cesarean may recur. Operative reports from prior surgery are requested when possible. The risks and benefits of TOLAC vs scheduled cesarean are reviewed as well as St. Luke's protocol for TOLAC (needs IV, clear liquid diet, continuous fetal monitoring, etc). To gauge preferences, contingency plans are discussed— what may happen if an induction is recommended or she remains pregnant beyond 39 weeks, 40 weeks, etc. Women do not need to commit to TOLAC or ERCD but are encouraged to think it over if undecided. If a patient has any interest in TOLAC, she is given a handout describing risks and benefits and a TOLAC consent form to review and bring back to a future visit (ideally with one of the obstetricians). If she is certain about pursuing TOLAC, she can sign the consent form that day.

Marin Community Clinic. At Marin Community Clinics, obstetric patients initiate care with an RN whose scope of practice includes intake examinations, patient triage, and initial review of laboratory and diagnostic results. At the intake appointment, the obstetric nurse reviews the patient's medical and obstetric history, initiates routine initial laboratory studies, and provides the patient with educational material. Most of the patients seen at our site, which is a Federally Qualified Health Care Center, are eligible for Medi-Cal, so the obstetric nurse also ensures that the patient begins the insurance eligibility process. After this initial intake appointment, patients are referred for an initial appointment with an obstetric provider who might be a nurse midwife, a family practice physician, or a nurse practitioner. Patients with complicated medical issues are referred to the two obstetricians who serve as consultants to the other providers.

Patients with a prior cesarean section are screened for PROCEED eligibility and participation in the study is discussed by the obstetric nurse at the initial intake appointment. Patients are also identified and screened during their subsequent visits with obstetric providers. The Site Principal Investigator is informed when a patient would like to participate and forwards demographic information for these patients to the PROCEED Study Coordinator who contacts the patients for interviews.

All patients who have had a prior cesarean and are eligible for a TOLAC are counseled regarding mode of delivery for their current pregnancy. A significant number of our patients are Spanish speaking and are scheduled between 24 and 34 weeks for a monthly group class in Spanish on the risks and benefits of TOLAC versus elective repeat cesarean section. The class consists of a group session followed by individual appointments with an obstetrician to address patient concerns and preference for mode of delivery. Patient who are English-speaking or speak another language are scheduled for an individual consultation with an obstetrician. Patients who elect trial of labor after cesarean are seen again to review their delivery plan if they have not yet delivered after 39 weeks. Patients who elect repeat cesarean are scheduled for an obstetric visit at 36 weeks to schedule a repeat cesarean section at 39 weeks.

Chicago, Illinois

Northwestern University Medical Center. Women who establish prenatal care at ambulatory practices associated with Northwestern Memorial Hospital are most often seen in the first trimester for a first obstetrical visit. An initial intake is conducted at which medical, surgical and obstetric histories are taken. Most obstetric providers are physicians, although there are groups with midwives as well, and in those groups patients who are eligible for care with either type of provider largely self-select into physician vs. certified nurse midwifery care. Providers review operative reports for prior cesareans if available. Discussions about delivery approach typically begin on the first prenatal visit and may be revisited throughout the course of the pregnancy. If elective repeat cesarean delivery (ERCD) is preferred, or even considered, a slot on the OR schedule is often reserved, at whatever gestational age and date are deemed acceptable and appropriate after conversations between the patient and provider.

Boston, Massachusetts

Massachusetts General Hospital. Women who establish prenatal care at Massachusetts General Hospital are typically seen between 8 and 12 weeks for a first obstetrical visit. An initial intake is conducted by a practice nurse at most sites, and often by phone at the largest site. During the initial intake, medical, surgical and obstetric histories are collected for new patients and are updated for returning patients. Prior pregnancy history is noted, including gestational age, pregnancy complications and modes of prior deliveries. Patients largely self-select into physician vs. certified nurse midwifery care, though access to physician care may be somewhat restricted to those with medical or obstetrical complexities at the three community health centers where prenatal care is provided. Operative reports for prior cesareans are reviewed for hysterotomy type, with findings documented in the problem list in the electronic medical record; attempts are made to obtain outside records for surgeries not performed at MGH or within the Partners Healthcare system. Discussions about approach of delivery generally begin as early as at the first prenatal visit and are revisited throughout the course of the pregnancy. Risks and benefits of trials of labor after cesarean are reviewed in detail and women's preferences, even if provisional, are recorded in their problem lists. Calculation and documentation of the likelihood of successful vaginal birth after cesarean using the "MFMU calculator" is common but not universal. If elective repeat cesarean delivery (ERCD) is preferred, or even considered, a slot on

the OR schedule is often reserved, at whatever gestational age and date are deemed acceptable and appropriate after conversations between the patient and provider. The primary provider will often schedule a time when s/he is available. For patients desiring ERCD who are enrolled in midwifery care, a visit with a physician provider is often scheduled prior to the planned delivery date. For women considering TOLAC, risks and benefits of induction of labor are reviewed should indication (including post-term pregnancy) arise. In the third trimester, women sign written informed consent for care on Labor and Delivery, including for repeat cesarean delivery or TOLAC where applicable.

Note: At all study sites, usual care for women with a prior cesarean includes counseling by the provider regarding mode of delivery. No formal educational intervention, web tools, or decision support is in place at any site. Use of the NICHD VBAC prediction tool is at the discretion of the prenatal provider.

15.2. Intervention

The Prior Cesarean Decision app (Appendices 1 and 2) includes the following features: 1) approximately 15 minutes of web-based content, 2) topic-specific content and graphics, 3) user-specific risk data presented in a dynamic and interactive environment, and 4) content in both English and Spanish. The program is organized into segments and sub-segments that are interactive and sequenced. To create a satisfying user experience and enhance user interaction, some segments include “learn more” buttons to access additional content. Users enter clinical information and responses to values clarification exercises, taking advantage of the mHealth platform to increase patient engagement while targeting both intuition and deliberation to optimize the effectiveness of decision support.[29]

The app was developed using a process based on the International Patient Decision Aids Standards Collaboration (IPDAS) quality checklist[30] to confirm that the content, development process, and effectiveness of the Prior Cesarean Decision app conform to the highest standards. Published data, as well as our own testing of prior interactive multimedia decision tools, provided the foundation for the content and framework for the Prior Cesarean Decision app.

Focus groups and one-on-one interviews were conducted at all sites prior to initiation of enrollment for the RCT. Women of varying literacy levels who were patients of the institution and had a prior cesarean section within the past three years were invited to participate in a one-time 60-90 minute feedback session with study personnel in which they completed a basic demographics questionnaire and were shown various versions of the app during the development process. The sessions were audio recorded and staff took notes of specific feedback to incorporate into the app. The app developers also attended some sessions to hear directly from potential future users. Participants were remunerated $60 for their participation.

16.0 STUDY PROCEDURES

16.1. Overview

The RC will perform a preliminary eligibility screening by chart audit of all women seeking prenatal services at the site (see section 5.1.1.). Women with one prior cesarean who speak English or Spanish and do not appear to have any contraindications to VBAC will be identified and approached for in-person eligibility review.

Women will be approached in the clinic waiting area before a prenatal appointment, informed of their potential eligibility for the study, and asked to complete and return a printed copy of the

opt-in form (see section 5.1.2,). If time permits and the woman is eligible and interested in participating, screening, enrollment, and randomization will take place same-day and immediately after the opt-in form is completed.

All study instruments will be administered in the language preferred by the participant, English or Spanish. A baseline screening form will be completed to verify the woman's eligibility, then written informed consent obtained from those eligible and interested in participating. Participant sociodemographic characteristics, expected due date, and current preference as to delivery approach will be collected using a baseline questionnaire. The participant will then be randomized to app (intervention) or no app (control). Participants randomized to app will be provided an iPad tablet pre-loaded with the app to view at their own pace (see sections 4.2 and 5.1.3. for more information). A short health literacy assessment will be administered after the app. Apart from the app, the intervention arm will receive usual care. A woman randomized to no app will complete the baseline questionnaire including the health literacy assessment, and will not view the app.

Patient-reported secondary outcomes will be assessed at 34 weeks 0 days to 37 weeks 6 days gestation through a phone follow-up interview administered by an interviewer blinded to the randomization group of the participant (see section 5.1.4.). After delivery, chart review will be performed by a blinded co-investigator to ascertain the primary outcome of delivery approach (TOLAC or ERCD), the secondary outcome of delivery mode (vaginal or cesarean) and any contraindications to TOLAC that developed post-randomization (see section 5.1.5.). Research assistants will also review the chart to collect other clinical data from the delivery encounter including the secondary maternal and neonatal morbidity outcomes.

Participants will receive $40 in remuneration for participating in the baseline screening and enrollment interview and $40 for participating in the phone follow-up interview. Participants who deliver at an outside institution will be contacted by telephone to collect self-reported delivery outcome and other pregnancy and delivery information as well as permission for release of the medical record (see section 5.1.6.).

16.1.1. Chart audit (<25 weeks gestation)

The medical charts of women who will be <25 weeks gestation at the next prenatal visit to the site will be reviewed for eligibility by a RC or provider at the site. Women with one prior cesarean who speak English or Spanish and have no contraindications to VBAC will be flagged for further in-person eligibility review.

16.1.2. Opt-in form (<25 weeks gestation)

Women flagged for follow-up according to the chart audit will be approached in the clinic waiting area before the prenatal appointment or told about the study by the provider during an OB visit. Women interested in participating will be asked to complete and return a printed copy of the opt-in form (Appendices 3 and 4). If the woman meets gestational age criteria for baseline screening (see section 5.1.3) and has enough time to complete the baseline screening and enrollment interview (approximately 15 minutes), the screening questionnaire can be administered on the same day (see section 5.1.3.). Otherwise, she will be contacted by the RC to schedule the screening in conjunction with an upcoming prenatal visit. A record of every woman approached will be kept in a REDCap database.

16.1.3. Baseline screening and enrollment interview (12 weeks 0 days to 24 weeks 6 days gestation)

Screening Questionnaire. In-person screening for eligibility will be administered by tablet when the woman is between 12 weeks 0 days and 24 weeks 6 days gestation, usually immediately after the opt-in form is collected. Eligibility will be assessed using a seven-question screening questionnaire (Appendices 5 and 6). A woman will be confirmed eligible if she self-reports all of the following: (1) a due date corresponding to a gestational age of 12 weeks 0 days to 24 weeks 6 days at time of interview, (2) carrying a singleton pregnancy, (3) a single prior cesarean section, (4) a cesarean section at her most recent delivery, (5) the cesarean section was not 'classical', i.e., the cut on the uterus does not run up and down, (6) does not recall any other uterine surgeries that would make her ineligible for a cesarean section, e.g. a myomectomy for removal of uterine fibroids, (7) planning to deliver at the current institution. Responses to the screening questionnaire will be collected in a REDCap database.

Consent. After the screening, printed informed consent and permission for release of medical records will be obtained from eligible participants using the consent and HIPAA forms (Appendices 7-10; see sections 8.2 and 8.3 for more information).

Baseline Questionnaire. The baseline questionnaire (Appendices 11 and 12) will be administered by tablet after consent. This form collects participant age, race/ethnicity, education, income, form of health insurance, estimated due date, and current preference for delivery approach. A print copy of the questionnaire will be offered to the participant to follow along as questions are read aloud (Appendix 13). The RC will keep track of the time at the start and end of the interview and note if there is an interruption to the interview lasting more than 5 minutes. The RC will also record if anyone is with the participant during the interview. Questionnaire data will be collected in a REDCap database.

Randomization and intervention. Treatment group will be assigned according to a randomization table in REDCap generated by the statistician co-investigator. If randomized to app, the participant will be given a tablet to view the app at her own pace (Appendices 1 and 2). The app will provide information on potential maternal and neonatal complications from vaginal and cesarean deliveries, values clarification questions, and an individualized estimate of the likelihood of a successful TOLAC. After viewing the app, a printed summary sheet with her answers to the values clarification questions and probability of successful TOLAC will be provided to each participant to take home (Appendices 14 and 15). More information about the app is provided in section 4.2. A participant randomized to the control arm will not view the app. If she inquires about the intervention, she will be told it consists of standardized information about the benefits and risks of trial of labor and elective cesarean.

Health Literacy Assessment. The interview will conclude with a short health literacy assessment (Appendices 11 and 12) which evaluates a woman's ability to interpret a nutritional label. The assessment will be completed by both treatment arms.

Remuneration and follow-up reminder. Women who complete the baseline interview will receive $40 in remuneration in the form of a gift card (Appendices 16 and 17) or check.

16.1.4. Phone follow-up interview (34- to 37 weeks gestation)

The Phone Follow-up interview will be completed with participants in both arms of the study between 34- and 37 weeks 6 days gestation. The goal of this interview is to collect data on the secondary study endpoints of knowledge about TOLAC and ERCD; decisional conflict; shared decision-making regarding delivery approach; decision self-efficacy; and decisional satisfaction.

Chart audit. Before contacting a participant, the RC will review her chart to establish whether she is still pregnant, has already delivered, or has experienced pregnancy loss before 22 weeks.

Phone interview. If the participant has not yet delivered, she will be contacted by the RC at 33 weeks gestation to schedule a time for the phone follow-up interview. A copy of the phone follow-up questionnaire (Appendices 18 and 19) will be offered to the participant by email or mail so she may follow along as questions are read aloud. The questionnaire will be administered by a different interviewer and collected in a separate REDCap database than the baseline questionnaire to ensure the interviewer remains blinded to the participant's randomization assignment (Appendix 24).

The phone follow-up interview will consist of: (1) a six-item short form of the Spielberger State-Trait Anxiety Inventory, which assesses the woman's general anxiety level[31], (2) eight questions to assess the woman's knowledge of TOLAC and ERCD adapted from a published questionnaire [32], (3) a 16-item Decisional Conflict Scale[33], (4) an 11-item Decisional Self-Efficacy scale[34], (5) a single-item assessment of the woman's preferred role in the decision-making concerning her delivery approach[35], (5) a 9-item shared decision making questionnaire (adapted from the SDM-Q-9[36]), and (6) a six-item Satisfaction with Decision Scale[37]. More information about these survey instruments can be found in section 7.1.2.

During the phone follow-up interview, the woman will be asked where she plans to deliver. If at an outside institution, the RC will request the participant's consent to be contacted again for the post-delivery questionnaire and to have a copy of her delivery record forwarded to the study team (see section 5.1.6.).

If the participant is no longer pregnant at the time of the phone follow-up interview, the RC will administer an abbreviated form of the phone follow-up questionnaire documenting where the woman delivered, date of delivery, delivery approach, and method of delivery. Women who had a loss before 22 weeks will not be contacted for a phone follow-up interview.

Remuneration. Women who complete the telephone interview will receive $40 in remuneration in the form of a gift card or check.

16.1.5. Chart audits (after delivery)

Participant charts will be reviewed after delivery to abstract delivery approach, delivery mode, and other clinical data (Appendices 20 and 21). Abstraction of delivery outcome data and any contraindications to TOLAC before delivery will be performed by a PI, co-investigator or research coordinator who is blinded to the randomization assignment. Other data from the delivery encounter, including maternal and neonatal morbidities and findings from the cervical exam at time of admission, will be abstracted by the RC. Data will be collected in REDCap. A comments box on the data collection form will allow RCs to document challenges interpreting the chart, which can also be raised at a coordinator call or addressed to a co-investigator or PI if necessary.

Investigator review. For investigator review of outcomes, the delivery note may provide clarity; in other cases, review of both the labor and delivery and prenatal record will be necessary. Whether the patient developed an absolute contraindication to TOLAC before her delivery admission may be obtained from the op note. Breech, Previa, or any congenital anomaly not compatible with vaginal delivery should be documented. To establish planned approach for the current delivery, the investigator will use the following definitions:

- Participant planned ERCD if:
    - Delivered by scheduled ERCD at 39 weeks prior to labor for no reason other than desired RCD rather than TOLAC
    - Presented in labor prior to scheduled cesarean, and opted to proceed with cesarean for primary reason that desired RCD rather than TOLAC

- Presented with indication for delivery prior to scheduled cesarean (preeclampsia, IUGR, NRFT) and opted to proceed with cesarean for primary reason that desired RCD rather than TOLAC

  Note: If there are two indications for RCD in the chart, including a nonelective indication for timing of delivery less than 39 weeks, the investigator will code the first as the "nonelective" indication and the second as ERCD.

- Participant considered TOLAC if:
  - Underwent TOLAC
  - Planned TOLAC if labor prior to certain gestational age, but reached that gestational age limit and underwent ERCD
  - Planned TOLAC if spontaneous labor, but then developed an indication for induction and underwent ERCD

16.1.6. Post-delivery phone interview for outside deliveries (after due date)

If a participant's due date has elapsed by more than three weeks and there is no record of the delivery at the site, she has likely delivered at an outside institution. In such cases, the RC will contact the participant by phone or email to set up a time for the post-delivery phone interview. During the interview, the participant will be queried for self-report of the date of delivery, delivery approach and mode, and other pertinent information such as whether the outside facility offers TOLAC, whether the woman experienced contractions or rupture of membranes, use of pitocin for labor augmentation, use of forceps or vacuum to assist with delivery, baby's birthweight, maternal weight gain during pregnancy, and other information. In addition, the RC will request the name of the outside institution where the woman delivered and her permission to contact the institution for release of her delivery record. Responses will be collected using the post-delivery questionnaire (Appendices 22 and 23) and stored in a REDCap database (Appendix 24).

17.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

17.1. Safety Monitoring and Clinical Data Review

A multi-tiered safety review process will be followed for the duration of this study. Close cooperation between the principal investigator, site principal investigators and other co-investigators, project manager, study coordinators, study statistician, and other study team members will be necessary to monitor participant safety and to respond to concerns in a timely manner. The investigative team will have monthly conference calls during the period of study implementation and additional ad hoc calls will be convened as needed.

RCs will report all participant complaints to the investigative team. These will be discussed during weekly/biweekly RC calls and monthly investigator calls.

Each study site is responsible for continuous close monitoring and management of adverse events (AE) in accordance with the protocol for AE reporting at their home institution (Appendices 28-30). The study site PIs are responsible for the initial evaluation and reporting of safety information and for alerting the investigative team if unexpected concerns arise.

17.2. Reporting Requirements for this Study

The site PI or RC will report an adverse event to the local IRB if study staff determines it may qualify as an Unanticipated Problem or Adverse Event because the event meets all three criteria listed below:

- Unanticipated in severity or frequency AND
- At least *possibly* related to the study intervention AND
- Is Serious OR not serious but suggests placing subjects or others at greater risk

In addition, all SAEs will be reported to the study team within 72 hours of recognition by study staff.

18.0 STATISTICAL CONSIDERATIONS

18.1. Endpoints

18.1.1. Primary Endpoint

Consistent with the primary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will be more likely to undergo TOLAC compared to women who receive only usual care, the following endpoint will be assessed in the medical record for the delivery:

- Proportion of women who elect TOLAC

18.1.2. Secondary Endpoints

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will be more likely to have a VBAC compared to women who receive only usual care, the following endpoint will be assessed in the medical record for the delivery:

- Proportion of women who have a VBAC

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will be more knowledgeable about TOLAC and ERCD and their potential outcomes compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Knowledge about TOLAC and ERCD and their potential outcomes, as assessed with a modified version of a published questionnaire.[32]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will experience less decisional conflict compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Decisional conflict regarding delivery approach, as measured based on the participant's score on a well-validated Decisional Conflict Scale[33] recommended for the assessment of decision quality by the IPDAS.[38] This measure generates an overall conflict score and 5 subscale scores and has been used extensively to evaluate patient-centered decision tools in a wide range of clinical contexts.[39]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will report higher levels of shared decision making regarding delivery approach compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Shared decision making, as measured using the SDM-Q-9, a psychometrically evaluated self-assessment tool.[36]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will experience greater decision self-efficacy compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Decision self-efficacy, as measured using a validated 11-item Decisional Self-efficacy Scale.[34]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will report higher levels of decision satisfaction compared to women who receive only usual care, the following endpoint will be assessed at weeks 34- to 37 gestation:

- Decisional satisfaction, as measured using the Satisfaction with Decision Scale, a 6-item scale designed to measure global satisfaction with a decision and to differentiate this from related aspects of satisfaction.[37]

Consistent with the secondary study hypothesis that women who are randomized to use the Prior Cesarean Decision app will experience lower rates of maternal and neonatal morbidity compared to women who receive only usual care, the following endpoints will be assessed in the medical record for the delivery:

- Maternal major morbidity, defined as any of: uterine rupture, hysterectomy, surgical injury (bowel, bladder/ureter, or other), maternal death.
- Maternal minor morbidity, defined as any of: blood transfusion, postpartum febrile morbidity (endometritis, cellulitis, urinary tract infection, or other infection)
- 3rd or 4th degree lacerations
- Neonatal death or HIE, defined as any of: stillbirth/fetal demise (antepartum or intrapartum), neonatal death, HIE
- Neonatal respiratory morbidity, defined as any of: respiratory morbidity requiring CPAP or intubation
- Neonatal intensive care unit (NICU) admission

18.2. Sample Size

Table 1 shows the minimum difference in TOLAC due to the Prior Cesarean Decision app that has 80% power. For a recruitment goal of 1,320 participants (1:1 per intervention arm) and assuming 5% loss to follow-up and a baseline rate of 33% in the control group, we will have at least 80% power to detect an 8% absolute increase in TOLAC due to the app.

Table 1: Minimum detectable effects for randomization α=.05, two-sided, power = 80%. LTFU = lost to follow-up rate.

Outcome	Assumptions	Effect Measure	N=1,200	**N=1,320**	N=1,440	N=1,660
TOLAC	Baseline rate (33%) LTFU (5%)	Absolute increase (%)	8%	**8%**	7%	7%

18.3. Blinding

Assessors of the primary and secondary outcomes will remain blinded to the randomization assignment throughout the study. The study participant and the RC who administers the baseline screening and enrollment interview will be aware of the participant's randomization assignment. Phone follow-up questionnaires and chart audits will be administered by a different interviewer and collected in a separate database than the baseline questionnaire to ensure the interviewer remains blinded to the participant's randomization assignment during collection of study endpoints.

18.4. Data Analysis

We will present sample characteristics by treatment assignment in the form of n's and %'s for categorical variables and means/standard deviations or medians and interquartile ranges for continuous variables.

For our primary outcome TOLAC and major secondary outcome VBAC, we will calculate the proportion with the outcome by treatment arm and test for differences between treatment arms using a Poisson regression model which has been adjusted for recruitment site and language of interview and includes robust standard errors. Comparisons will be presented in the form of relative risks and 95% confidence intervals. Differences between treatment arms for the maternal and neonatal morbidity outcomes will be evaluated in the same manner. For continuous outcomes (e.g., decisional conflict, shared decision making regarding delivery approach, decision self-efficacy, and decisional satisfaction), we will calculate the mean score by treatment arm and test for differences using linear regression models adjusted for recruitment site and language of interview.

For our primary outcome TOLAC and major secondary outcome VBAC, we will examine interactions of treatment arm by the a priori defined factors of site, race/ethnicity, and language. For each interaction, differences will be evaluated using a Poisson regression model with an interaction term for treatment arm by subgroup.

Analyses will exclude women who had a pregnancy loss before 22 weeks gestation. We will also perform a sensitivity analysis of TOLAC and VBAC rates and differences in TOLAC and VBAC between treatment arms after excluding women who develop placenta previa or breech presentation.

19.0 HUMAN SUBJECTS CONSIDERATIONS

19.1. Ethical Review

Informed consent forms will pass through review and approval by the local IRB. as will participant education and recruitment materials, any other documents requested by the IRB, and any subsequent modifications to a document after approval. Review will be with respect to scientific content and compliance with applicable research and human subjects regulations.

IRB review of the study protocol will occur at least annually. The Site PI or RC will provide safety and progress reports to the IRBs at least annually and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

19.2. Informed Consent

Written informed consent will be obtained from each study participant prior to enrollment using an informed consent form approved by the local IRB in accordance with all applicable regulations. A copy of her signed informed consent form will be offered to the participant (Appendices 7 and 8).

19.3. HIPAA

Permission for release of medical records for ascertainment of clinical endpoints will be obtained from participants with the Health Insurance Portability and Accountability (HIPAA) form, which documents the personal health information that may be released, to whom it may be released, how it may be used, when permission for its release expires, and under what terms permission may be cancelled (Appendices 9 and 10).

19.4. Risks

Breach of confidentiality. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others. We are evaluating a mobile health intervention linked to a cloud platform and there is the possibility that study participation could become known to others despite the use of firewalls, password protection, and other security measures.

19.5. Benefits

Participation in the intervention arm of this study may lead to improved rates of TOLAC and other beneficial outcomes as posited in sections 2.1 and 2.1 of this manual. There may be no direct benefits to participants in the control arm of this study; however, they and others may benefit in the future from information learned from this study.

19.6. Incentives

Participants will be compensated for their time and effort in this study through remuneration of $40 following participation in the baseline interview and $40 following participation in the phone follow-up questionnaire. Remuneration will be the in the form of a gift card (Appendices 16 and 17) or check.

19.7. Confidentiality

All study-related information will be stored securely at the study site in locked file cabinets or on password-protected databases managed in accordance with section 9.1.3. of this study protocol. Participant study information will not be released without the written permission of the participant except as necessary for monitoring by the NIH and/or the site IRB.

20.0 ADMINISTRATIVE PROCEDURES

20.1. Study Coordination

Study implementation will be directed by this study protocol. Study case report forms and other study instruments are attached as Appendices 1-32. Protocols for training and study team communication are covered in sections 9.1.1. and 9.1.2. Section 9.1.3 reviews database management and data quality monitoring plans. Use of information is described in Section 9.1.4.

20.1.1. Trainings

The project manager at UCSF will train the RCs and other project staff at each of the sites. Topics covered will include:

- Study background, justification & aims
- Inclusion & exclusion criteria, eligibility screening
- Participant tracking in REDCap
- Appointment scheduling
- Approaching potentially eligible participants
    - Etiquette for in-person approach in the clinic waiting bay
    - Opt-in/opt-out forms
- Informed consent
- Randomization protocol
- Questionnaires
    - Baseline face-to-face questionnaire
    - Phone follow-up questionnaire
- Equipment
    - iPads
    - Portable Wi-Fi-enabled color printers
- Chart review
- Remuneration

20.1.2. Study Communication

Calls and in-person meetings will be scheduled throughout the study period to ensure clear communication, collegial collaboration, and rapid response to any challenges that may arise.

Investigator Calls.

The PI will lead monthly conference calls with the site PIs, co-investigators, project manager, and data manager. Topics to be discussed will include:

- Project timelines
- Recruitment plans
- Enrollment and retention reports
- Study design and implementation
- Questionnaire revisions (as necessary)
- Data analysis plans, progress and results
- Manuscript and abstract plans and progress
- Review of draft manuscripts and abstracts
- IRB renewals and modifications
- Budgets and contracts
- Other study management issues as needed

Research Coordinator Calls.

The project manager at UCSF will hold weekly 30-minute phone calls with the research coordinators for the first six months of the project. After six months, they will switch to a bi-weekly conference call schedule. The PI or a site PI will participate as needed. Coordinator calls will cover the following topics:

- Current totals interested, scheduled for enrollment, enrolled, scheduled for phone follow-up, followed-up, charts reviewed, by site
- Successes, challenges, and new ideas for:
    - Screening and approaching patients
    - Reaching recruitment targets
    - Utilizing technology (iPads, printers, Wi-Fi)
    - Administering questionnaires
    - Interfacing with the app
    - Scheduling and coordinating follow-up interviews and chart reviews
    - Carrying out follow-up interviews and chart reviews
    - IRB modifications
    - Other issues as needed

Annual Meetings.

Each year, the PI will host an annual in-person meeting of one- to two days with the site PIs, co-investigators, project manager, data manager, and RCs. Topics covered will be similar to the monthly calls but with time for lengthier discussion. Parallel break-out sessions for investigators and staff may be held to cover topics relevant to each group. A meeting of the PI and site PIs may also take place to discuss confidential matters and critical leadership/management decisions. A second annual meeting for broader visioning of scientific goals and dissemination plans will be held in-person among study members attending the annual Society for Maternal Fetal Medicine conference.

20.1.3. Database Management and Data Quality Monitoring

Randomization assignment, survey responses, and chart audit data for all sites will be collected and stored in REDCap databases hosted centrally at UCSF. Data will be behind an institutional firewall and accessible through a web portal via login credentials known only to qualified study staff. Randomization assignment will be collected in a separate database than the phone follow-up questionnaire and chart audits to ensure staff remain blinded to treatment group while gathering outcome data. Sites will maintain their own tracking and recruitment logs in local REDCap databases (Appendix 24). Protected health information, such as patient names, medical record number, estimated due date, clinic visit schedule, telephone number and email address will be collected on the tracking and recruitment log to aid with scheduling and participant follow-up. A unique study identifier will be generated for each participant to link records across databases.

Data from the app will be collected through a secure, password-protected online portal linked to a PostGRE SQL database on a Heroku cloud platform, which provides best-in-class server security, including firewalls, physical security, and regular compliance auditing.

Clinical, survey and app data will be transferred to SAS statistical software for cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the study sites on a routine schedule for verification and resolution.

20.2. Use of Information and Publications

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. Presentation and publication of the results of this study will be governed by guidelines determined by the study team and as necessary and appropriate by their associated institutions policies. Any presentation, abstract, or manuscript will be approved by the protocol chair prior to submission.

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22.0 APPENDICES

	Document	Version Date
1	App PDF-English	112015
2	App PDF-Spanish	112015
3	Opt-in form-English	111615
4	Opt-in form-Spanish	112015
5	Screening questions-English	111615
6	Screening questions-Spanish	112015
7	UCSF Consent-English	111615
8	UCSF Consent-Spanish	112015
9	UCSF HIPAA-English	111615
10	UCSF HIPAA-Spanish	112015
11	Baseline Questionnaire-English	111615
12	Baseline Questionnaire-Spanish	112015
14	App summary sheet-English	111615
15	App summary sheet-Spanish	112015
16	UCSF Gift Card Receipt-English	111615
17	UCSF Gift Card Receipt-Spanish	112015
18	Phone Follow-up Questionnaire-English	111615
19	Phone Follow-up Questionnaire-Spanish	112015
20	Chart Review tool (investigator)	111615
21	Chart Review tool (RC)	111615
22	Post Delivery Phone Questionnaire for Outside Deliveries-English	111615
23	Post Delivery Phone Questionnaire for Outside Deliveries-Spanish	112015
24	RedCap tracking & recruitment log data dictionary	010416
25	IRB/CHR Approval Letter-UCSF	121415
26	IRB Approval Letter-California Pacific Medical Center	091718
27	IRB Approval Letter-Massachusetts General	121815
28	IRB Approval Letter-Northwestern	121015
29	IRB Adverse Event Reporting-Northwestern	111315
30	IRB Adverse Event Reporting-Mass. General	111315
31	IRB Adverse Event Reporting-UCSF	111315