Parent Education and Choice about Newborn Screening and Bloodspot Retention

NHGRI Grant Number: 1RO1HG006266

Principal Investigator: Jeffrey R Botkin

NHGRI Program Official: Joy Boyer

Draft or Version Number: 1.0

January 28, 2016
STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.
SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: ___________________________________________ Date: 1/29/16

Name: Jeffrey R. Botkin, MD, MPH

Title: Professor of Pediatrics
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LIST OF ABBREVIATIONS

AE                Adverse Event/Adverse Experience
CFR               Code of Federal Regulations
DHHS              Department of Health and Human Services
FDA               Food and Drug Administration
ICH               International Conference on Harmonisation
IDE               Investigational Device Exemption
IND               Investigational New Drug Application
IRB               Institutional Review Board
NIDCR             National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH               National Institutes of Health
SAE               Serious Adverse Event/Serious Adverse Experience
US                United States
# PROTOCOL SUMMARY

**Title:** Parent Education and Choice about Newborn Screening and Bloodspot Retention  

**Précis:** A randomized control trial with women in their third trimester of pregnancy, that viewed multimedia education materials during a prenatal care visit. Baseline demographic data was collected during the prenatal visit and a telephone survey was conducted 2-4 weeks after their expected due date. Analysis of variance (ANOVA) will be used with the dependent variables. A sensitivity analysis was conducted with the following assumptions: sample size of each group = 240, Alpha = 0.05, Power = .85, and Two-tailed testing, results showed we will be able to detect a small effect size (Cohen’s d=0.25). Again, if group equivalency is not shown, we will add variables as covariates to the modeling.

**Objectives:**

Primary: *To determine the impact of the prenatal education intervention on parental knowledge, attitudes, and decisions regarding NBS services and the retention and use of residual samples in diverse populations of English and Spanish speaking pregnant women.*

Secondary: NA

**Population:** Eight hundred and seventy women in the third trimester of pregnancy with no reported complication in Utah, California and New York

**Phase:** NA

**Number of Sites:** Intermountain Healthcare, Salt Lake City, Utah  
Montefiore Medical Center, Bronx, New York  
University California San Francisco

**Description of Intervention:** A multimedia intervention, two movies and two brochures. One on Newborn screening and the other on Newborn Dried blood spots.

**Study Duration:** 18 months

**Subject Participation Duration:** Less then one hour

**Estimated Time to Complete Enrollment:** 12 months
Schematic of Study Design:

1.4 Enrollment

- Approached (n=1247)
  - Declined to participate (n=345, 28%)
  - Enrolled (n=902, 72%)
    - Randomized (n=901, 72%)

1.1 Allocation

- Standard of Care (n=305, 34%)
- NBS video (n=300, 33%)
- NBS + DBS videos (n=296, 33%)

1.2 Analysis

- Standard of Care (n=212, 70%)
- NBS video (n=231, 77%)
- NBS + DBS videos (n=221, 75%)

1.3 Follow-Up

- Standard of Care (n=212, 70%)
- NBS video (n=231, 77%)
- NBS + DBS videos (n=221, 75%)
1 KEY ROLES AND CONTACT INFORMATION

| Principal Investigator:                  | Jeffrey R. Botkin, MPH MD |
| Medical Monitor:                         | none                      |
| NHGRI Program Official:                  | Joy Boyer                 |
| Clinical Site Investigators:             | Siobhan Dolan MD, Montefiore Medical Center  
                                         | Miriam Kuppermann PhD, University California San Francisco  
                                         | Nancy Rose MD, Intermountain Health |
| Institutions:                           | University of Utah, Montefiore Medical Center, University California San Francisco, Intermountain Health |
| Other Key Personnel:                    | Rebecca A. Anderson, RN PhD  
                                         | Erin Rothwell, PhD  
                                         | Louisa Stark, PhD  
                                         | Bob Wong, PhD |
2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

It is widely recognized that new parents receive insufficient information about newborn screening (NBS) and little or no information regarding the retention of residual newborn screening samples. Our current research (R01 HD058854) clearly demonstrates that parents are supportive of NBS and the research use of residual specimens, but they want information before the child is born and want an informed choice regarding the retention and use of residual samples. Previous research has outlined the basic elements of what parents want to know about NBS generally. However, given that many states are adopting an “opt-out” approach for residual samples, it is unclear what basic information parents want to know to enable an informed choice about this practice. While it is recognized that retention and use of residual NBS samples is a valuable research resource, there are prevalent concerns in the NBS community that discussion of this will lead some parents to decline NBS altogether. Some authorities have suggested that discussions of NBS and residual sample retention be conducted separately to reduce the risk that parents will confuse the issues and decline NBS altogether.

2.2 Rationale

Our current research (R01 HD058854) clearly demonstrates that parents are supportive of NBS and the research use of residual specimens, but they want information before the child is born and want an informed choice regarding the retention and use of residual samples. Previous research has outlined the basic elements of what parents want to know about NBS generally. However, given that many states are adopting an “opt-out” approach for residual samples, it is unclear what basic information parents want to know to enable an informed choice about this practice.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The risks in this study are minimal. The risks are similar to other information about procedures given to pregnant women and their partners given prenatally and will occur during the birth (i.e. blood cord, placenta donation).

2.3.2 Potential Benefits

There are substantial benefits to society for improving the public health program of newborn screening. Identifying ways to better inform parents about this mandated public health program
will improve parental understanding and may improve the use of residual bloodspots for important health research. Participants may receive benefits from improved knowledge about newborn screening, However, there may be no direct benefits to participants.
3 OBJECTIVES

3.1 Study Objectives

To address the content, timing, efficacy, and impact of prenatal education about newborn screening generally and sample retention specifically, this project has the following specific aims:

- To determine the impact of the prenatal education intervention on parental knowledge, attitudes, and decisions regarding NBS services and the retention and use of residual samples in diverse populations of English and Spanish speaking pregnant women.

- To examine the normative/ethical implications of the results of SA3 for the conduct of state NBS programs. Recommendations on the content and timing of parental NBS education will be developed.

3.2 Study Outcome Measures

3.2.1 Primary

Hypothesis) Women in all groups will be similarly supportive of newborn screening programs. Increased knowledge of NBS programs could lead to either an increase or a decrease in support for the programs. Health care information in general is usually not associated with a decline in support for health care programs. Therefore we hypothesize that a new exchange of information in the prenatal period will not lead to a decline in the currently high levels of support for NBS programs.

Analysis: Just as the previous hypothesis, we will run a series of ANOVA’s. The dependent variable will be participant’s attitude toward NBS programs, and the independent variable will remain as group membership. Covariates will be added if warranted. Sensitivity analysis replicated above results, sufficient power to detect small effects.

Hypothesis) Women in the prenatal intervention groups A and B will not differ significantly in their choices about 1) retention of residual specimens, or 2) participation in NBS, than women who do not receive the multimedia interventions (control). Increased knowledge of NBS programs and about residual specimens could lead to concerns about sample retention and decisions to opt-out of sample retention or NBS altogether. However, a discussion of the relevant benefits and risks of sample retention may lead to reassurance and acceptance of the practice. Therefore we will adopt the null hypothesis that a new exchange of information in the prenatal period will not lead to an increase in the number of parents who opt-out of sample retention or NBS.

Analysis: We will calculate the percentage of opt-outs for each of the three groups, and utilize pair-wise comparisons with Z-tests of proportions to investigate statistical significance. To insure an adequately powered study, we utilized GPower (Version 3.1) to estimate sample size. The
following assumptions were made: the base rate of opting out (Control condition) = 2%, the rate of opting out to detect = 7% (Video condition, an increase in 5% over base). One-tailed testing, alpha=0.05, and power = 0.85. Results show a sample size of 240 total for intervention and control groups would be sufficient. If covariates are needed, identified by our initial group equivalency tests, we will shift our analyses to a logistic regression model, loading in covariates as potential predictors.

### 3.2.2 Secondary

**Hypothesis 2)** **Women in all groups will be similarly supportive of newborn screening programs.** Increased knowledge of NBS programs could lead to either an increase or a decrease in support for the programs. Health care information in general is usually not associated with a decline in support for health care programs. Therefore we hypothesize that a new exchange of information in the prenatal period will not lead to a decline in the currently high levels of support for NBS programs.

**Analysis:** Just as the previous hypothesis, we will run a series of ANOVA’s. The dependent variable will be participant’s attitude toward NBS programs, and the independent variable will remain as group membership. Covariates will be added if warranted. Sensitivity analysis replicated above results, sufficient power to detect small effects.

**Hypothesis 3)** **Women in the prenatal intervention groups A and B will not differ significantly in their choices about 1) retention of residual specimens, or 2) participation in NBS, than women who do not receive the multimedia interventions (control).** Increased knowledge of NBS programs and about residual specimens could lead to concerns about sample retention and decisions to opt-out of sample retention or NBS altogether. However, a discussion of the relevant benefits and risks of sample retention may lead to reassurance and acceptance of the practice. Therefore we will adopt the null hypothesis that a new exchange of information in the prenatal period will not lead to an increase in the number of parents who opt-out of sample retention or NBS.

**Analysis:** We will calculate the percentage of opt-outs for each of the three groups, and utilize pair-wise comparisons with Z-tests of proportions to investigate statistical significance. To insure an adequately powered study, we utilized GPower (Version 3.1) to estimate sample size. The following assumptions were made: the base rate of opting out (Control condition) = 2%, the rate of opting out to detect = 7% (Video condition, an increase in 5% over base). One-tailed testing, alpha=0.05, and power = 0.85. Results show a sample size of 240 total for intervention and control groups would be sufficient. If covariates are needed, identified by our initial group equivalency tests, we will shift our analyses to a logistic regression model, loading in covariates as potential predictors.
4 STUDY DESIGN

• This study is a randomized control trial.
• The population is pregnant women in their third trimester with not reported pregnancy complication.
• Our current research (R01 HD058854) clearly demonstrates that parents are supportive of NBS and the research use of residual specimens, but they want information before the child is born and want an informed choice regarding the retention and use of residual samples.

• Study Groups
  o **Group A**: pregnant women who will view the NBS and residual specimen movies and printed materials during one visit between 30 and 40 weeks (N= 240 total, 80 per site).
  o **Group B**: pregnant women who will view the NBS movie only and printed materials at one visit between 30 and 40 weeks (N= 240 total, 80 per site). The movies will be presented on a tablet PC.
  o **Control Group**: pregnant women who will receive no experimental intervention during pregnancy or the postpartum period but will receive whatever information is routinely provided by their OB clinic and/or delivery center (n=240 total, 80 per site).

• Approximate time to complete study enrollment is 12 to 18 months
• The expected duration of subject participation is 6 to 12 weeks
• If the woman is eligible and interested in participating, a coordinator will approach potential participants at her clinic visit to schedule a time to obtain her consent. After the participants sign informed consent, the RC will collect baseline data (contact information and demographics). Participants then will be randomized to three study groups. **Group A**: pregnant women who will view the NBS and residual specimen movies and printed materials during one visit between 30 and 40 weeks (N= 240 total, 80 per site). **Group B**: pregnant women who will view the NBS movie only and printed materials at one visit between 30 and 40 weeks (N= 240 total, 80 per site). The movies will be presented on a tablet PC. **Control Group**: pregnant women who will receive no experimental intervention during pregnancy or the postpartum period but will receive whatever information is routinely provided by their OB clinic and/or delivery center (n=240 total, 80 per site). Participants will be encourage, through the interventional materials, too share the information provided with their partners and discuss NBS and use of residual specimens with them. Participants also may present questions or concerns to their OB care providers who will be provided a general education about the issues before recruitment begins.

• Timing of the intervention during the clinic visit may be variable and will depend on the normal workflow in the OB clinic. We will utilize a time when women are waiting
before or between interactions with the physician or nurse. Participants will be in a quiet
room or taken to a private room that will be conducive to learning and allow them to
focus on the intervention, given an IPad, and instructed in its use. Women will view the
multimedia presentation at their own pace (the presentation can be paused) and clinic
staff or the RC will be available to assist with machine operation or questions about the
content. The presentations (one on NBS and one on Residual Specimens) will each be
approximately 6 minutes in length. Based on Kuppermann’s experience, we anticipate
that these presentations can be made during typical waiting times without disruption of
normal clinic routines, although we will evaluate whether this is the case by
interviewing clinic staff at the completion of the intervention. Clinic flow will be
organized such that participants do not lose their place in the queue for care. Follow up
telephone interviews will be conducted 2-4 weeks after you give birth. Dan Jones will
conduct the follow up interviews.
5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

Inclusion criteria include for this phase of the project is adult (≥ 18 years) English and Spanish speaking women with full-term pregnancies who have give birth.

A total of 150 partners of women who complete the post-natal survey will be recruited, with approximately 50 partners from each recruitment site.

5.2 Subject Exclusion Criteria

Women age 18 and older are adults in each of our recruitment sites so pregnant women younger than age 18 at the time of recruitment will be excluded. This exclusion is due to the potentially confounding effect of other social factors for adolescent mothers.

5.3 Strategies for Recruitment and Retention

For the New York and California sites, the Research Coordinators will review clinic charts to identify pregnant patients who are approaching their 28th gestational week to identify eligible participants. Letters describing the study will be sent to all women who appear to meet entry criteria, and will include the Research Coordinator telephone number and an “opt in/out” card, which the participant can mail back. A Research Coordinator (RC) will contact patients who check “opt in,” or who do not return the card, at one of their next visits to the clinic to discuss the study and assess eligibility and interest in participating. The letter will be written at the fifth-grade level and translated into Spanish. Patients who are interested will complete an opt-in card, which the site coordinator will use to contact them and arrange a baseline interview. When mail or telephone contact is not feasible, women attending their 30th to 40th week prenatal visit will be informed of the study by the clinic staff and interested participants will be contacted by a coordinator.

The Utah Intermountain Healthcare site has a daily presence in the Avenues Women’s Center office. We will approach all apparently eligible women at one of their appointments before their 30-week appointment with an information sheet about the study; this is a routine approach that we have used in this office repeatedly for other projects. We will schedule a convenient time to obtain written consent and authorization between 30-40 weeks gestation. At the time of consent and authorization, the participant will be randomized and the appropriate intervention will be administered either at the same time or at their next visit, (at whatever time the participant prefers).
5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures (if applicable)

5.4.2 Masking Procedures (if applicable)

NA

5.5 Subject Withdrawal

5.5.1 Reasons for Withdrawal

Subjects may withdraw from the study voluntarily. They may not be able to contact for the f/u survey or they may refuse to participate in the f/u survey.

5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

Demographic data will not be included in final data set.

5.6 Premature Termination or Suspension of Study

If a significant number of mothers report opting out of newborn screening.
6 STUDY INTERVENTION

6.1 Screening

For the New York and California sites, the Research Coordinators will review clinic charts to identify pregnant patients who are approaching their 28th gestational week to identify eligible participants. Letters describing the study will be sent to all women who appear to meet entry criteria, and will include the Research Coordinator telephone number and an “opt in/out” card, which the participant can mail back. A Research Coordinator (RC) will contact patients who check “opt in,” or who do not return the card, at one of their next visits to the clinic to discuss the study and assess eligibility and interest in participating. The letter will be written at the fifth-grade level and translated into Spanish. Patients who are interested will complete an opt-in card, which the site coordinator will use to contact them and arrange a baseline interview. When mail or telephone contact is not feasible, women attending their 30th to 40th week prenatal visit will be informed of the study by the clinic staff and interested participants will be contacted by a coordinator.

The Utah Intermountain Healthcare site has a daily presence in the Avenues Women’s Center office. We will approach all apparently eligible women at one of their appointments before their 30-week appointment with an information sheet about the study; this is a routine approach that we have used in this office repeatedly for other projects. We will schedule a convenient time to obtain written consent and authorization between 30-40 weeks gestation. At the time of consent and authorization, the participant will be randomized and the appropriate intervention will be administered either at the same time or at their next visit, (at whatever time the participant prefers).

6.2 Enrollment/Baseline

If the woman is eligible and interested in participating, a coordinator will approach potential participants at her clinic visit to schedule a time to obtain her consent. After the participants sign informed consent, the RC will collect baseline data (contact information and demographics). Participants then will be randomized to three study groups. Group A: pregnant women who will view the NBS and residual specimen movies and printed materials during one visit between 30 and 40 weeks (N= 240 total, 80 per site). Group B: pregnant women who will view the NBS movie only and printed materials at one visit between 30 and 40 weeks (N= 240 total, 80 per site). The movies will be presented on a tablet PC. Control Group: pregnant women who will receive no experimental intervention during pregnancy or the postpartum period but will receive whatever information is routinely provided by their OB clinic and/or delivery center (n=240 total, 80 per site). Participants will be encourage, through the interventional materials, too share the information provided with their partners and discuss NBS and use of residual specimens with them. Participants also may present questions or concerns to
their OB care providers who will be provided a general education about the issues before recruitment begins.

Timing of the intervention during the clinic visit may be variable and will depend on the normal workflow in the OB clinic. We will utilize a time when women are waiting before or between interactions with the physician or nurse. Participants will be in a quiet room or taken to a private room that will be conducive to learning and allow them to focus on the intervention, given an IPad, and instructed in its use. Women will view the multimedia presentation at their own pace (the presentation can be paused) and clinic staff or the RC will be available to assist with machine operation or questions about the content. The presentations (one on NBS and one on Residual Specimens) will each be approximately 6 minutes in length. Based on Kuppermann’s experience, we anticipate that these presentations can be made during typical waiting times without disruption of normal clinic routines, although we will evaluate whether this is the case by interviewing clinic staff at the completion of the intervention. Clinic flow will be organized such that participants do not lose their place in the queue for care. Follow up telephone interviews will be conducted 2-4 weeks after you give birth. Dan Jones will conduct the follow up interviews.

6.3 Final Study Visit

Follow up telephone interviews will be conducted 2-4 weeks after you give birth. Dan Jones will conduct the follow up interviews.
7 STUDY PROCEDURES /EVALUATIONS

7.1 Study Procedures/Evaluations

• Baseline survey conduct in prenatal clinic collecting demographic information

7.2 Laboratory Procedures/Evaluations

NA
8 ASSESSMENT OF SAFETY

Specification The number of mothers reporting that they child did not have newborn screening will be monitored. If a significant number reports this the study will be halted until the cause is determined.

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

8.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
• Results in a congenital anomaly or birth defect

• An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
   a. The event is known to occur with the study intervention.
   b. There is a temporal relationship between the intervention and event onset.
   c. The event abates when the intervention is discontinued.
   d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)
   a. There is no temporal relationship between the intervention and event onset.
   b. An alternate etiology has been established.

8.2.1 Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.2.2 Severity of Event

The following scale will be used to grade adverse events:
1. Mild: no intervention required; no impact on activities of daily living (ADL)

2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL

3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

8.3 Reporting Procedures

The PI will immediately report, no more then 24 hours of any adverse event to the University of Utah IRB with the intuitions reporting forms.

8.3.1 Unanticipated Problem Reporting to IRB and NIDCR

Incidents or events that meet the OHRP criteria for unanticipated problems a unanticipated problem report form will be completed. The OHRP recommendations that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB will be done:

- appropriate identifying information for the research protocol, such as the title, investigator’s name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDCR within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB’s receipt of the report of the problem from the investigator.

8.3.2 Serious Adverse Event Reporting to NHGRI
Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to NHGRI’s Program Officer. This report may be sent by fax or email. Once submitted, the study clinician will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

8.3.3 Reporting of SAEs and AEs to FDA

NA

8.3.4 Events of Special Interest (if applicable)

NA

8.3.5 Reporting of Pregnancy

NA

8.4 Halting Rules

The studies recruitment will be halted if a significant number of mothers report their child did not have NBS, >10%.
9 STUDY OVERSIGHT

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of the Key personnel of the team composed of members with expertise in, statistical, scientific, ethical. The Research team will meet monthly to assess safety and efficacy data (if applicable), study progress, and data integrity for the study. If safety concerns arise, more frequent meetings may be held.
10 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the key personnel at the University of Utah. The monitor will evaluate study processes and document progress.
11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Hypothesis 1) Women in the prenatal intervention groups will demonstrate higher knowledge in newborn screening than women who do not receive the multimedia interventions (control). The intervention involves a multimedia presentation "The 7 things parents want to know about NBS" and "the X things parents want to know about residual sample retention" as determined in SA1. Women in the prenatal time period will be more “teachable” about newborn screening compared to women in the postnatal environment due to the greater demands on the mother’s time, attention, and energy following the birth of their baby. From an adult learning perspective and the theoretical constructs of Social Cognitive Theory, changing the environment in which learning takes places from postpartum to the prenatal period should increase receptiveness, attention span and retention, and will result in greater knowledge about NBS.

Analysis: Analysis of variance (ANOVA) will be used for this hypothesis. The dependent variable will be knowledge, and the independent variable of interest will be group membership (Group A, Group B, or Control). Again, if group equivalency is not shown, we will add variables as covariates to the modeling.

Hypothesis 2) Women in all groups will be similarly supportive of newborn screening programs. Increased knowledge of NBS programs could lead to either an increase or a decrease in support for the programs. Health care information in general is usually not associated with a decline in support for health care programs. Therefore we hypothesize that a new exchange of information in the prenatal period will not lead to a decline in the currently high levels of support for NBS programs.

Analysis: Just as the previous hypothesis, we will run a series of ANOVA’s. The dependent variable will be participant’s attitude toward NBS programs, and the independent variable will remain as group membership. Covariates will be added if warranted. Sensitivity analysis replicated above results, sufficient power to detect small effects.

Hypothesis 3) Women in the prenatal intervention groups A and B will not differ significantly in their choices about 1) retention of residual specimens, or 2) participation in NBS, than women who do not receive the multimedia interventions (control). Increased knowledge of NBS programs and about residual specimens could lead to concerns about sample retention and decisions to opt-out of sample retention or NBS altogether. However, a discussion of the relevant benefits and risks of sample retention may lead to reassurance and acceptance of the practice. Therefore we will adopt the null hypothesis that a new exchange of information in the prenatal period will not lead to an increase in the number of parents who opt-out of sample retention or NBS.

Analysis: We will calculate the percentage of opt-outs for each of the three groups, and utilize pair-wise comparisons with Z-tests of proportions to investigate statistical significance. To insure an adequately powered study, we utilized GPower (Version 3.1) to estimate sample size. The following assumptions were made: the base rate of opting out (Control condition) = 2%, the rate of opting out to detect = 7% (Video condition, an increase in 5% over base). One-tailed testing, alpha=0.05, and power = 0.85. Results show a sample size of 240 total for intervention and control groups would be sufficient. If covariates are needed, identified by our initial group
equivalency tests, we will shift our analyses to a logistic regression model, loading in covariates as potential predictors.

Hypothesis 4) Partners of women in the intervention groups A or B will not differ in knowledge or attitudes regarding NBS or bloodspot retention compared to partners of women in the control group. Partners of participants may or may not receive secondary information from pregnant women who participate in the study therefore we will adopt a null hypothesis.

Analysis: Analysis of variance will once again be employed to investigate the relationship of partner's knowledge and attitudes regarding NBS to treatment assignment of the women.

Prior to analysis we will test for group equivalency on basic demographic variables (age, race, ethnicity, site, etc.) to insure our randomization process was effective. If significant differences exist, we may include those variables as covariates in our models.

Based on these assumptions and calculations, we plan to recruit a sufficient number of participants to obtain 80 completed survey responses per site from each of the 3 intervention groups for a total of 240 participants per site. Recruitment site will have a sufficient number of participants to enable a robust comparison between groups within each site. The overall goal for the study is 720, from the three sites, completed surveys. We estimate a 20% dropout rate between enrollment and completion of the final survey instrument. This estimate is based on the experience of Kupperman and colleagues using a similar methodology. Therefore our recruitment goal for each site will be 300 for a total study recruitment goal of 900 women.

Furthermore we will recruit a subset of partners of the pregnant women who have agreed to participate. When mothers are surveyed post partum their partners will be invited by the survey company to participate and complete a survey similar to the one the mothers will answer. A key question is whether partners of women who did receive education differ from partners of women who did not receive education in terms of knowledge and attitudes about NBS and sample retention. That is, do partners receive education from the pregnant woman on these topics? Our recruitment goal is 150 partners (75 from intervention groups and 75 from controls with approximately 50 from each recruitment site) which will enable the detection of a small to medium effect size, Cohen’s d=.5.

11.2 Sample Size Considerations

A sensitivity analysis was conducted with the following assumptions: sample size of each group = 240, Alpha = 0.05, Power = .85, and Two-tailed testing, results showed we will be able to detect a small effect size (Cohen’s d=0.25).
11.3 Planned Interim Analyses (if applicable)

Ongoing analysis of mother that report their infant did not receive NBS will be conducted.

11.3.1 Safety Review

During monthly review of the mothers that report their infants did not have NBS if greater then 10% of the total sample recruiting will be halted.

11.3.2 Efficacy Review

NA

11.4 Final Analysis Plan

Analysis of variance (ANOVA) will be used for the hypothesis. Again, if group equivalency is not shown, we will add variables as covariates to the modeling.
12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NHGRI and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.
13 QUALITY CONTROL AND QUALITY ASSURANCE

Each site will have standard operating as describe:

- How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
- Recruitment logs and baseline patient surveys will be monitored.
- Dr. Bob Wong will monitor quality of the data collection and intervention administration.
- Staff training methods and how such training will be tracked.
- If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.
14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children younger then 18 and mothers that do not speak English or Spanish will be excused.
14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

14.6 Future Use of Stored Specimens and Other Identifiable Data

NA
15 DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities
Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.2 Data Capture Methods
Ongoing electronic data collection into REDCap, a research data management platform will be conducted.

15.3 Types of Data
Demographic and outcome measures data will be collected.

15.4 Schedule and Content of Reports
Enrollment, survey completion and adverse events reports will be generated and reviewed at least monthly by the PI and research team.

15.5 Study Records Retention
Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

15.6 Protocol Deviations
A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.
These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to NHGRI and the local IRB, according to their requirements.
16 PUBLICATION/DATA SHARING POLICY

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](http://www.ncbi.nlm.nih.gov/pmc) upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as [ClinicalTrials.gov](https://clinicaltrials.gov), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee’s responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.
17 LITERATURE REFERENCES


Institute of Medicine. (2010). Challenges and Opportunities in Using Residual Newborn


Rothwell, E. (2007). Understanding community perspectives on research usage for residual blood samples (University of Utah Genesis Center Focus Group Project). Salt Lake City, UT.


SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

No additional materials are needed for the protocol, beyond what is included in this document.