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Complete List of Authors:	Dempsey, Amanda; University of Colorado Denver, USA, Wagner, Nicole; Kaiser Permanente Colorado,, Institute for Health Research Narwaney, Komal; Kaiser Permanente Colorado, Institute for Health Research Pyrzanowski, Jennifer; University of Colorado Denver Kwan, Bethany; University of Colorado School of Medicine, Family Medicine Kraus, Courtney; Kaiser Permanente, Institute for Health Research Gleason, Kathy; Kaiser Permanente Colorado , Institute for Health Research Resnicow, Ken; University of Michigan, Health Education and Health Behavior sevick, carter; University of Colorado Denver Cataldi, Jessica; University of Colorado Denver Brewer, Sarah; University of Colorado Denver Glanz, Jason M; Kaiser Permanente Colorado, Institute for Health Research
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The "Reducing Delays in Vaccination" (REDIVAC) Trial: A protocol for a randomized controlled trial of a web-based, individually tailored, educational intervention to improve timeliness of infant vaccination

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Amanda F. Dempsey[1] - Amanda.dempsey@ucdenver.edu

Nicole Wagner[2] - Nicole.M.Wagner@kp.org

Komal Narwaney[2] - Komal.J.Narwaney@kp.org

Jennifer Pyrzanowski[1] - Jennifer.pyrzanowski@ucdenver.edu

Bethany Kwan[1] - BETHANY.KWAN@UCDENVER.EDU

Courtney Kraus[2] - Courtney.Kraus@kp.org

Kathy Gleason[2] - Kathy.s.Gleason@kp.org

Kenneth Resnicow[3] - kresnic@umich.edu

Carter Sevick[1] - CARTER.SEVICK@UCDENVER.EDU

Jessica Cataldi[1] - Jessica.Cataldi@childrenscolorado.org

Sarah Brewer[1] - SARAH.BREWER@UCDENVER.EDU

Jason Glanz[2] - Jason.M.Glanz@kp.org

Affiliations:

[1] Adult and Child Consortium for Outcomes Research and Delivery Science (ACCORDS), University of Colorado Denver, Aurora, CO

[2] Kaiser Permanente Colorado Institute for Health Research, Denver CO

[3] School of Public Health, Division of Health Behavior and Health Education, University of Michigan, Ann Arbor, MI

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Abstract

Introduction:

Increasing numbers of children are failing to receive many recommended vaccines, which has led to significant outbreaks of vaccine preventable diseases in the US and worldwide. A major driver of undervaccination is parental vaccine hesitance. Prior research demonstrates that mothers are the primary decision maker for infant vaccination, and that their vaccination attitudes form primarily during pregnancy and early in their infant's life.

Methods and Analysis:

This manuscript describes the protocol for an ongoing 3-armed, randomized controlled trial that aims to test the efficacy of provided tailored, individualized information via the internet to pregnant and new mothers versus untailored information versus usual care on the timeliness of infant vaccination. The primary outcome to be assessed is vaccination status, which is a dichotomous outcome (up to date versus not) assessed at 200 days of age, reflecting the time when infants should have completed the first set of vaccine provided (at age 2, 4 and 6 months). Infants with one or more age-appropriate recommended vaccines at least 30 days delayed are categorized as not up to date whereas all other infants are considered up to date. Secondary outcomes include vaccination status at 465 days, reflecting receive of recommended vaccines at 12-15 months of age, as well as vaccination attitudes, hesitancy and intention. Vaccination data will be derived from the electronic medical record and the state immunization registry. Other secondary outcomes will be assessed by online surveys.

Ethics and Dissemination:

The study activities were approved by the Institutional Review Boards of the University of Colorado, Kaiser Permanente Colorado, and the University of Michigan. Results will be disseminated through peer reviewed manuscripts and conference presentations.

Article Summary:

Strengths and Limitations of the Study:

- **Strength:** Randomized, controlled trial design
- **Strength:** Population based sample
- **Strength:** Longitudinal analysis of EMR data
- **Limitation:** Only one geographic area limits generalizability

Trial Registration: This trial has been registered at ClinicalTrials.gov - NCT02665013.

Key words: vaccine hesitancy; immunization; mothers; clinical trial

Introduction

Vaccination has been touted as one of the most effective public health interventions ever created.[1] Despite this, increasing numbers of parents choose to delay or forgo recommended vaccines for their children because of uncertainty about the vaccines' safety and necessity and general mistrust of the pharmaceutical industry.[2,3] With this, increasing numbers of children are failing to receive many recommended vaccines, which has led to significant outbreaks of vaccine preventable diseases in the US and worldwide.[4,5]

Developing and evaluating interventions to counteract parental vaccine hesitancy and childhood under-vaccination is a public health priority.[6] While many prior interventions have been tested, the majority have not been effective.[7-9] Addressing vaccine hesitancy can be difficult and time consuming because parents' vaccination decisions are often complex as they are heavily influenced by emotion, past experiences, and peers.[10-12] Addressing this complexity can be difficult for health care providers who attempt to persuade parents to vaccinate their children,[13] given that typical pediatric clinical encounters last only 15 to 20 minutes. As a result, even when parents only have a few questions that might be easily answered, a provider may feel "burnt out" when having to discuss vaccines with questioning parents.[14] In addition, in many cases the resistance to vaccination is related to psychosocial and political beliefs as much, or even more than, knowledge deficits.

Given this, new approaches to address vaccine hesitancy that are time efficient and address the complex factors influencing vaccine decision-making are needed.[15] One promising approach is

to use message tailoring to provide parents with information about vaccines that is customized to their own personal needs *before* their child's clinical appointments. Message tailoring allows for written information to be individualized to reflect each person's unique beliefs, experiences, knowledge, attitudes, and barriers to action.[16] By doing so, the personal relevance of the information increases which in turn improves individuals' receptiveness to that information – this is especially important in the case of vaccine hesitancy when the new information may not align with a person's current attitudes or beliefs.[16] This approach has been shown to be effective for improving compliance with a number of health behaviors but only minimally applied to vaccination. [17,18]

This manuscript describes the protocol for a 3-armed randomized controlled trial testing the effectiveness of a web-based tailored messaging intervention called "Vaccines and Your Baby" (VAYB) versus an untailored version of the intervention versus usual care for improving timely uptake of recommended childhood vaccines.

Conceptual Model

The conceptual model for the intervention is based on a hybrid of the theory of planned behavior (TPB) and the value-attitude-behavior hierarchy model (Figure 1).[19,20] It also incorporates strategies derived from motivational interviewing and self-affirmation.[21,22] According to the TPB, behavior (in this case, following the recommended vaccination schedule) is influenced by intentions (in this case, vaccine hesitancy), which are a result of attitudes towards the behavior, perceived behavioral control, and norms. This intervention primarily

focuses on strategies for influencing attitudes – i.e., tailored messages addressing individual behavioral beliefs (e.g., beliefs that immunity is best achieved through exposure to a pathogen, or "natural immunity") framed according to personal values (e.g., emphasizing the benefits of vaccination for preventing spread of illness among the young and elderly for those who value protecting one's community). By affirming individual patient values and identity, addressing autonomy (Motivational interviewing and Self Determination Theory)[21,23] and constructing controlling tones of messages, this can minimize reactance and counterarguments. Individually tailored messages in general are known to have greater effects on attitude change than are universal (untailored) messages.[20,24,25] According to the value-attitude-behavior hierarchy model[26], values influence attitudes and behavior across cultures and domains, including recycling, consumer behavior, and alcohol consumption.[27,28] This hybrid approach to establishing the conceptual model allows us to focus the intervention strategies on addressing a select set of known determinants of vaccine hesitancy and behavior, rather than incorporating the universe of behavior change techniques into our intervention.

Aim and Hypothesis

The primary aim of this study is to conduct a three-group randomized, intervention trial to measure the effectiveness of the VAYB intervention versus a similarly constructed but untailored intervention versus usual care on vaccination receipt and timeliness during an infant's first 15 months of life. Our intervention approach (the VAYB intervention) is novel in that it combines values framing with message tailoring for vaccination to change parents' attitudes and behavior. The primary hypothesis to be tested is that infants of mothers who

receive values-framed, individually tailored messages (e.g. the VAYB intervention) will have lower levels of vaccine hesitancy and more up to date vaccination behavior than those receiving an untailored version of the intervention or those receiving usual care. A secondary aim of the project is to assess the impact of the intervention on vaccination attitudes and hesitancy level, particularly as these relate to our conceptual model described above.

Methods

A summary of the trial's specifications is shown in Table 1.

Study Design and Registration

This is a 3-armed, individually randomized clinical trial with longitudinal follow up. Study arms include 1) the VAYB (tailored) intervention, 2) an untailored version of the intervention and 3) usual care. Participants are active in the study from the time of enrollment until their infant reaches 15 months of age (489 days). The primary vaccination outcome to be assessed for the study (average number of days under vaccinated for all vaccinations in the recommended vaccine schedule) occurs when the infant is 200 days old. Secondary vaccination outcomes and outcomes related to attitudes and hesitancy are assessed at 489 days of age. This time period was chosen to encompass three critical decision making points associated with the vaccination process; 1) during pregnancy when many vaccination decisions and attitudes are being formed;[29,30] 2) during the time period that corresponds to the ages when the initial infant series

is recommended (generally at ages 2, 4 and 6 months); and 3) during the second stage of the infant vaccination series at age 12-15 months when vaccines different from those offered at the initial stage are introduced. The primary outcome (vaccination behavior) is assessed using data from the electronic medical record, augmented with data from the Colorado immunization registry, CIIS. The study is registered with ClinicalTrials.gov (NCT02665013, see Table 1 for details).

Study Setting

The study takes place via the internet. Participants in the VAYB and untailored arms view educational materials on a web-enabled device or computer of their own and are prompted to view this information again at specific time points during the study (described below). Participants enrolled in the usual care arm receive by mail Vaccine Information Statements (VIS) for all recommended vaccines in the child's first year of life; VISs are not provided by mail to participants in the VAYB or untailored arms. Participants in all arms complete surveys at baseline, and three additional time points (Table 2). The infants of participants in all arms receive care at participating clinics (an eligibility criterion, see below) where VISs are provided to all study groups as part of routine care.

Study Population and Inclusion/Exclusion Criteria

Women in the third trimester of pregnancy enrolled at Kaiser Permanente Colorado (KPCO) between April 2016 and October 2017 are recruited for the trial. KPCO is a nonprofit, managed care organization serving ~667,000 individuals. Each year ~5,000 pregnant women and 140,000 children receive health care at KPCO clinics. Study participants can enroll from the first recruitment outreach that occurs in the last trimester of pregnancy to when their infant is ≤ 2 months of age. The infant must be enrolled in the KPCO health plan to continue participation in the study.

A combination of electronic medical record (EMR) data and study screening questions are used to determine study eligibility. First, the EMR is used to identify English speaking women, currently enrolled at KPCO, and ≥ 18 years of age in the last trimester of pregnancy, based on clinically determined expected delivery date. All identified women with a diagnosis (ICD10) code in the past 8 months indicating potential abortion, miscarriage, adoption, fetal anomalies, or genetic disorders in the pregnancy, or a high risk maternal condition (i.e. cancer) are flagged for potential exclusion. Medical chart reviews are conducted on these women and they are definitively excluded as potential participants if the EMR indicates their fetus has a high-risk condition (e.g., fatal heart condition, trisomy 18, anencephaly), or they have a spontaneous or elective abortion, social issues (such as domestic violence), or serious health concerns. Screening questions are delivered online before consent to ensure participants plan to use KPCO medical care for their child, are ≥ 18 years of age, and are currently pregnant or have a child less than 2 months of age. During the course of the study, participants are removed if they have a fetal demise, infant death, if the infant loses KPCO insurance coverage for greater

than 90 days, if they request to be removed from the study or if they die. This data is obtained from a monthly data extraction from the EMR and patient report.

Consent and Recruitment

Recruitment occurs via a multistep process. After the EMR is used to screen for initial eligibility, a series of 2 letters, 3 emails, and one phone call are sent to potential participants 1-2 weeks apart to direct patients to the KPCO study registration website created specifically for this study. On this registration website identity and eligibility are confirmed, and the participant is consented by signing an online form.

After consent participants are directed to the *study* website where they set up login information and are provided with a Pre-intervention Questionnaire that assesses their baseline intention to vaccinate, vaccination values, logistical barriers to vaccination, vaccine hesitancy (used for randomization), and demographics, and re-confirms eligibility. Previously developed and validated measures are used to assess these items.[31-33] Upon completion of this questionnaire, participants are considered to be "enrolled" in the study and are randomized (described below). The screening, consent and enrollment process is repeated monthly until the target sample size is reached.

Assignment of Interventions

Participants are randomized on a 1:1:1 basis between the VAYB, untailored and usual care arms. The allocation assignment is generated by back-end software embedded in the study website. Randomization occurs immediately following enrollment into the study (i.e. after completion of the pre-intervention questionnaire) and remains in place throughout the study. Stratified randomization along with a permuted block technique is used such that participants are first stratified into either a hesitant or non-hesitant group, based on responses to the pre-intervention questionnaire. Participants from each group are then added to their own set of blocks that each contain 6. There are 2 slots available for each of the 3 study arms. These slots are randomly ordered when the block is created. When all 6 slots are filled, a new block with 6 randomly ordered slots is added.

Blinding

Participants are not informed about which study arm they are assigned to but all three study arms they could potentially be assigned to are described in the study consent documents. Thus, although they are not told specifically which arm they are in, they are not blinded to their study assignment. The project manager for the study will convert study data to unlabeled arms (i.e. arm 1, 2 or 3) allowing for the rest of the study team to be blinded to study arm assignment during the analysis and data interpretation phases of the project. Unblinding will occur when data analysis is complete for the primary study outcome. Clinics where participants receive care are not aware of the individuals participating in the study unless brought up by the patient during a clinical encounter.

Sample Size Calculation

To detect an odds ratio between 2.0 and 3.0 for up-to-date vaccination status between the intervention study arms and usual care, we estimate a needed sample size of 477 to 1002 participants. This sample size is based on an assumption of 15% of the recruited population being vaccine hesitant, a 1:1:1 randomization allocation ratio, two-sided tests of statistical significance, 80% statistical power, and a 5% type I error rate. Accounting for an attrition of 15%, we need to enroll 561 to 1179 participants.

Interventions

Tailored Intervention

In the VAYB arm messages were tailored for multiple constructs including intention to vaccinate, personal attitudes about vaccines, vaccination values (Table 2), vaccination beliefs and concerns, logistical barriers to vaccination, and child's name, sex and birthday. Data to inform this initial tailoring come from the Pre-Intervention Questionnaire. Interim questionnaires are used to refresh the tailored information at 3 times during the study period. Tailoring occurs based on an embedded algorithm that is part of the VAYB website. An in-depth description of the process used to develop the VAYB intervention, and the resulting content, is described in detail elsewhere but examples are provided in Table 3.[32,33]

Upon completion of the pre-intervention questionnaire where initial tailoring information is obtained, participants are automatically directed to the VAYB website which is individually customized based on their responses. The most highly tailored content is in three "Just for You" tiles that are displayed prominently on the page (Figure 2A). These tiles reflect the top three vaccine topics of concern that each participant indicates they want more information about and are further customized to highlight the vaccination values the participant most endorses, and to reflect their most recently reported intention to vaccinate. The remaining content is lightly tailored to reflect participant's attitudes, concerns, hesitancy and demographics, but is not tailored based on vaccination values. Highlighted text on the home page (Figure 2A) is used to further identify additional information that is most relevant to the participant based on their survey answers. The website is refreshed 3 times during the course of the study based on interim assessments of participants' attitudes, beliefs, concerns, values and vaccine hesitancy. Specifically, when the infant is 4 to 6 months of age, participants re-answer all questions excluding the value items and questions used to assess vaccine hesitancy, and the content is refreshed accordingly. Values are reassessed again in a 3rd survey when the infant is 10 to 12 months and the website is refreshed to reflect any new content. Vaccine hesitancy level is reassessed at a 4th survey and the content is again refreshed. Participants receive a gift card after each survey is completed. For all time points, vaccination intention is assessed immediately before and within the hour after viewing the website content (VAYB and untailored arms). A reminder for this vaccination intention assessment is sent to non-responders after one day.

Untailored Intervention

To isolate the impact that message tailoring has on mothers' vaccination attitudes and behavior, the primary comparator group in the study is a website that is similarly constructed as the VAYB website but lacks tailored elements. Specifically, the untailored intervention has similar text, content and design as the VAYB intervention, but is not linked to survey responses to make the messages individually customized (Figure 2B). This means that each participant in this arm receives identical content, messages, text and images. For example, instead of name-tailoring, the text uses generic references such as "you" and "your child". The recommended vaccine schedule is static in the untailored site compared to the tailored site which highlights upcoming vaccines based on the child's age. The order of content displayed is fixed throughout the study period as there is no linkage of the website's text to participants' values or attitudes. In addition, the highly tailored "Just for You" tiles are not present in the untailored intervention. The same questionnaires administered to participants in the VAYB arm are administered to participants in the untailored arm, but the material is not used to refresh the website content

Usual Care

After taking the Pre-Intervention Questionnaire that is used to determine randomization, participants in the usual care arm are thanked for their information and logged off the study website. They receive an email containing their gift card and are mailed the Vaccine Information Statements for the vaccines due in the child's first year of life. They do not have access to the VAYB or untailored websites used for the other arms of the study but do receive

the same interim questionnaires at the same time periods as the VAYB and untailored arms (see Table 2). They continue their usual care and their infant's vaccination status is assessed prospectively when their child turns 200 days old (primary outcome) and again when their child is age 489 days (secondary outcome).

Routine pediatric care is available to infants of all participants in the study. At KPCO, usual care typically consists of a series of pediatric, well-child care visits at 2 weeks, 2 months, 4 months, 6 months, and 12 months of age, with an optional visit at 9 months of age if desired by the healthcare provider or parent. Visit content is structured based on the Bright Futures program of American Academy of Pediatrics, which provides detailed guidelines regarding the content and schedule of pediatric health supervision visits.[34] The visit content is intentionally broad, with visits focused on the needs of the child and family that typically last 20 minutes or less. Based on data in the EHR, a pre-visit informational sheet lists the vaccines recommended at that visit. Parents are also provided with the VISs relevant to that visit. Providers are often asked about vaccination, and can provide additional information verbally, although the small window of time available for visits can limit discussion.

Outcomes

The primary outcome of the study is a dichotomous categorization of vaccination status (up-to-date vs. not up-to-date) that is defined based on a continuous measure of days under-vaccinated. This outcome is assessed at 200 days of age to cover a majority of the initial infant vaccination series and to minimize the loss to follow-up. The following 6 vaccines

recommended by the Advisory Committee on Immunization Practices will be assessed: hepatitis B; rotavirus; diphtheria-tetanus-acellular pertussis; Haemophilus influenzae type b; pneumococcal conjugate vaccine; and polio. All vaccination data is obtained from KPCO's EMR CIIS.

To categorize vaccination status we will first assess the number of days under-vaccinated, by calculating the difference between when a vaccine dose was actually administered and when a vaccine dose should have been administered according to the vaccination schedule recommended by the Advisory Committee on Immunization Practices,[35] plus an additional 30 day "leeway" to account for vaccination that did not occur at exactly the minimal interval between doses. For example, the first dose of rotavirus vaccine is due at age 2 months (61 days) but is not considered late until age 92 days. Days undervaccinated for this dose begin accruing on day 93. The number of days under-vaccinated is then summed across all doses and vaccines to calculate a total number of days under-vaccinated for each infant and can range from 0-648 days. Infants with 0 total days undervaccinated at 200 days will be considered up-to-date on their vaccination status; Those with $\geq$1 days undervaccinated (representing at least a 30-day delay for at least 1 vaccine) will be considered not up-to-date.

A secondary vaccination metric that is assessed is up-to-date status for measles-mumps-rubella (MMR) and varicella vaccine at 489 days, when delay for the first dose of these vaccines begins. This metric is useful because it incorporates outcomes related to parents' decision-making

about these two vaccines recommended at 12-15 months of age that are not offered previously.

The interventions' impact over time on a variety of additional secondary outcomes that are based on the constructs of our conceptual behavioral model (Figure 1) and assessed as part of the baseline and interim questionnaires will also be assessed. These include changes over time in vaccination attitudes and hesitancy, and how these relate to study arm, vaccination values, and vaccination status. Vaccination attitudes are assessed using measures previously developed by our team and others,[31] values are assessed using a novel vaccination values framework we have developed (manuscript in preparation), and vaccine hesitancy is assessed using a 5-item validated measure developed by (Opel, personal communication). A variety of covariates and potential moderators will be assessed as part of this analysis including patient age, gender and insurance (some patients have Medicaid KPCO coverage), and mother's age, race, and ethnicity.

Data Collection Methods

Vaccination data is collected routinely as part of clinical care within the KPCO health system and will be assessed from the KPCO EMR data warehouse at pre-defined ages (200 days and 489 days). CIIS will be used as a secondary vaccination data source, though internal audits demonstrate that >95% of childhood vaccines given to KPCO patients are captured within the EMR. Survey data are collected on the internet based on user responses to the online questionnaires.

Participant retention

To assist with retention, participants receive a $20 gift card incentive for each survey they complete. However, even with this incentive we expect some drop off in survey participation. Because our primary outcome is vaccination status, mothers who do not participate in all the study surveys are still able to have the primary study outcome assessed, so long as their child maintains coverage and continues to seek care within the KPCO health system. Based on past studies, we expect that the proportion of mothers who discontinue KPCO coverage after the birth of their infant to be ~15%, and our study is powered with this attrition in mind.[36]

Data security and storage

To ensure that the data are protected, several methods are used. Personal identifying data collected on study websites is limited to a participant generated username, email address, and child birthdate. The only other data collected on the study websites are vaccine attitudes, beliefs, values and demographics. The study websites use virtualized servers housed at redundant data centers and access is password protected. Virtual servers are backed up automatically onto encrypted tape for recovery and security. Data provided to researchers from the website are encrypted if they are transmitted across the Internet. Data use agreements are in place across all study team member sites.

All medical record data are collected and stored at KPCO behind the firewall in secure password protected files. This dataset is linked to a study ID. A limited dataset devoid of personal identifying information will be used for data analyses. Data will be shared with study team members through a secure file transfer. Only members of KPCO research project team have access to the personal identifiers linking the study IDs to specific study participants.

Statistical Methods

Total days undervaccinated will be analyzed primarily as a dichotomous variable (up-to-date vaccination status) and secondarily as a continuous measure. Categorically defined up-to-date vaccination status will be analyzed using logistic regression to estimate odds ratios and associated 95% confidence intervals. For the continuous measure, because total days undervaccinated has a highly skewed distribution, we will use a nonparametric analysis and a rank transformation approach. For both measures, we will conduct analyses stratified by baseline vaccine hesitancy.

For survey measures, descriptive statistics will be assessed and changes in vaccination attitudes and intention over time will be calculated. All measures are assessed using Likert scales and will be analyzed as linear measures. Repeated measures ANOVA will be used to assess the intervention's impact on these outcomes. Mixed linear models will be used to assess the

"difference in difference" over time among these outcomes, by arm, controlling for the covariates described above.

Analytic framework

We will use a modified intention to treat framework for the analysis of vaccination outcomes. This analytic cohort will include infants of all randomized mothers who maintained KPCO health coverage for the allotted amount of time (200 days for the primary outcome, 489 days for the secondary outcome) with no more than 90 days of no coverage, and thus have vaccination data available for assessment. For survey outcomes, we will use a modified intention to treat analysis that includes all participants with data from at least one non-baseline questionnaire.

Missing data

As described above, nearly all vaccines provided to KPCO patients are documented in the EMR, and doses provided outside KPCO are documented in CIIS. Therefore, we expect there to be minimal missing data for vaccination outcomes. To ensure the most complete record, CIIS will be cross checked for all participants to identify any vaccine doses given to infants outside the KPCO system that are missing from the KPCO EMR. Participants who do not have vaccination data present in either system will be assumed to have not gotten a vaccine dose elsewhere.

For survey data, due to our recruitment strategy, we anticipate no missing data at baseline, as completion of the baseline survey was a criterion for entry into the study. However, there may be missing data for subsequent surveys as these were not required to remain in the study. For missing data in surveys beyond baseline, multiple imputation models will be developed for analyses involving multiple survey points where greater than 10% of subjects would be lost due to missing values.

Subgroup analyses

The main subgroup analysis planned is examining the efficacy of our intervention by vaccine hesitancy status (dichotomous variable), as defined by the 5 item Opel measure described above.

Monitoring

KPCO EMR data on participants and their infants will be used to identify any deaths or loss of KPO insurance coverage, which are subsequently chart reviewed for accuracy. Participants who die or experienced an infant death, or have >90 days loss of insurance coverage, will be removed from the study and will not be included in the modified intention to treat analysis. All participants will be monitored weekly for completion of the various surveys in the study and reminder emails will be sent on a pre-set schedule to those who have not completed them.

However, failure to complete any surveys beyond the baseline survey will not be cause for removal from the study.

Assessment of Harms and AEs

Study participants are provided with contact information for the research team and encouraged to contact the team if they experience any adverse events related to their participation in the study (e.g. being contacted after an infant death). Adverse events are expected to be very unlikely given the nature of the study and our monitoring procedures. However, should any significant adverse events occur, they will be reported to the appropriate institutional authorities.

Ethics and Dissemination

Approvals

This study is approved by the Institutional Review Boards at the University of Colorado, and KPCO.

Informed consent

All mothers in the study are informed about the study, the risks and benefits and provide written informed consent via an on-line registration process prior to participating in the study.

As part of the consent process participants are informed that they may withdraw from the study at any time without impacting their clinical treatment.

Access to data

The data will be accessed only by authorized persons directly involved in the study from the University of Colorado Denver, KPCO and University of Michigan. Access to a de-identified, aggregated version of the dataset and analysis code will be available upon request and approval of the study team

Competing Financial Interests

Amanda Dempsey serves on advisory boards for Merck, Pfizer, and Sanofi and as a consultant for Pfizer. She does not receive any research funding from these companies and they played no role in this project. All other research team members have no competing financial interests to declare.

Dissemination Plans

Results of the study will be presented at national and international research conferences and through peer-reviewed publications. Any changes to the study protocol will be clearly communicated to journals publishing the study results in a manner that aligns with the journal's policies for reporting clinical trials. CONSORT guidelines will be followed when reporting study

outcomes. Study materials such as questionnaires and screenshots of the intervention websites will be available to researchers upon request from the study Principal Investigators. If the VAYB intervention proves to be efficacious in reducing delays in the timeliness of infant vaccination, the study team will work with web-developers and community organizations to explore options to make the website available to the general public.

Patient and Public Involvement

Patients were first involved in this research when designing the intervention, which is informed by the literature, and by the research teams prior clinical and research experience. The bulk of patient involvement was as research participants. They will not be involved in recruitment or conduct of the study, data analysis, or dissemination.

Figure Legends

Figure 2: The right arrow denotes the "Just for You" tiles that represent the most highly tailored content on the VAYB website. The left arrow denotes additional text reflecting lightly tailored material that is particularly salient to the participant based on their survey responses.

Table 1. Trial Registration Dataset Summary Table

Data Category	Information
Registry and trial number	ClinicalTrials.gov - NCT02665013
Data of registration	1/4/2016
Secondary identifying numbers	CO-IRB #: CO-15-2299_07
Financial Support	National Institutes of Health
Contact for queries	Amanda.dempsey@ucdenver.edu
Title	The REDIVAC study-Reducing Delay in the Vaccination of Children
Countries of Recruitment	United States
Health condition studied	Infant vaccination
Interventions	Active comparator – tailored educational website Placebo comparator – untailored educational website Passive comparator – usual care
Key inclusion and exclusion criteria	Inclusion: ≥18 years, pregnant in 3rd trimester or child <2 months of age, receives care at KPCO health system, able to read English, access to the internet. Exclusion: high risk maternal or fetal health condition, maternal social issues (such as abuse), fetal or infant death, does not plan to have infant receive care in KPCO health system after birth

Study type	Individually randomized, controlled trial
Date of first enrollment	4/20/2016
Target sample size	700
Trial status	Ongoing data collection
Primary outcomes	Average days undervaccinated; Up to date vaccination status
Key Secondary Outcomes	Vaccination attitudes; Vaccination values; Vaccine hesitancy level

Table 2. Timing and Content of Study Questionnaires		
Timing	**Rationale**	**Content**
Last trimester of pregnancy or child <2 months of age	Pre-intervention questionnaire required for study enrollment. Our prior research indicates infant vaccination decisions are actively forming among expectant mothers.	Intention to vaccinate Vaccination values Vaccination attitudes Logistical barriers Vaccine hesitancy status Demographics
At child age 4 to 6 months	First round of infant vaccines is typically provided at age 2, 4 and 6 months. The same vaccines are given at each visit.	Intention to vaccinate Vaccination attitudes Logistical barriers Vaccine hesitancy (only 3 of 5 Qs)
At child age 10 – 12 months	The same vaccines are provided at 2, 4 and 6 months of age, thus decisions made at the two-month visit are likely to be followed for 4 and 6-month vaccines. However, several new vaccines are introduced at the 1-year visit. Vaccine-hesitant parents are	Intention to vaccinate Vaccination values Vaccination attitudes Logistical barriers Vaccine hesitancy status

	likely to need additional, new information for making decisions about the vaccines provided at age 1 year.	
Age 13-15 months	End of study assessment to track changes over crucial time periods of vaccine decision-making	Vaccination attitudes Vaccine hesitancy status Satisfaction with website

Table 3 Examples of VAYB Website Content for Two Topics, Showing Tailoring Based on Three Different Values

Vaccines and Your Baby: Tailored Messages		
Value	**Topics**	
	"Alternative /Delayed Vaccine Schedules" Message	**"Doing your own Research on Vaccines" Message**
Security – Disease Prevention	Like many parents, your main goal is to keep your child healthy. The last thing you want is for your child to get an illness you could have prevented with a simple vaccine.	You're the kind of person who will do everything she can to protect her baby from illnesses.
Self-Direction	You're not one to just do what other people tell you to do. You know your child better than anyone, and you have choices to make. You want to do your own research about vaccines. You don't want him/her to get a disease. But you don't want to put him/her at risk by getting vaccines.	You're the kind of person who plays an active role in decisions about her baby's health.
Security – Vaccine Risk	That's a lot of needles (and a lot of tears)! You want to protect your child. But with so many vaccines at once, you're concerned about exposing him/her to too many unnatural ingredients all at once.	You're the kind of person who will do everything she can to protect her baby from pain or unnecessary medicines.

Author Statement.

Amanda Dempsey, Nicole Wagner and Jennifer Pyrzanowski wrote the first draft of the protocol. All other authors reviewed the protocol and provided substantive edits and additions to the text, tables and/or figures.

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Competing Interests:

Amanda Dempsey serves on Advisory Boards for Merck, Pfizer and Sanofi Pasteur, and has provided consulting services to Pfizer. She does not receive any research funding from these companies. All other authors have no competing interests to declare.

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Figure 1: Model of parental vaccine values, vaccine attitudes, hesitancy and behavior

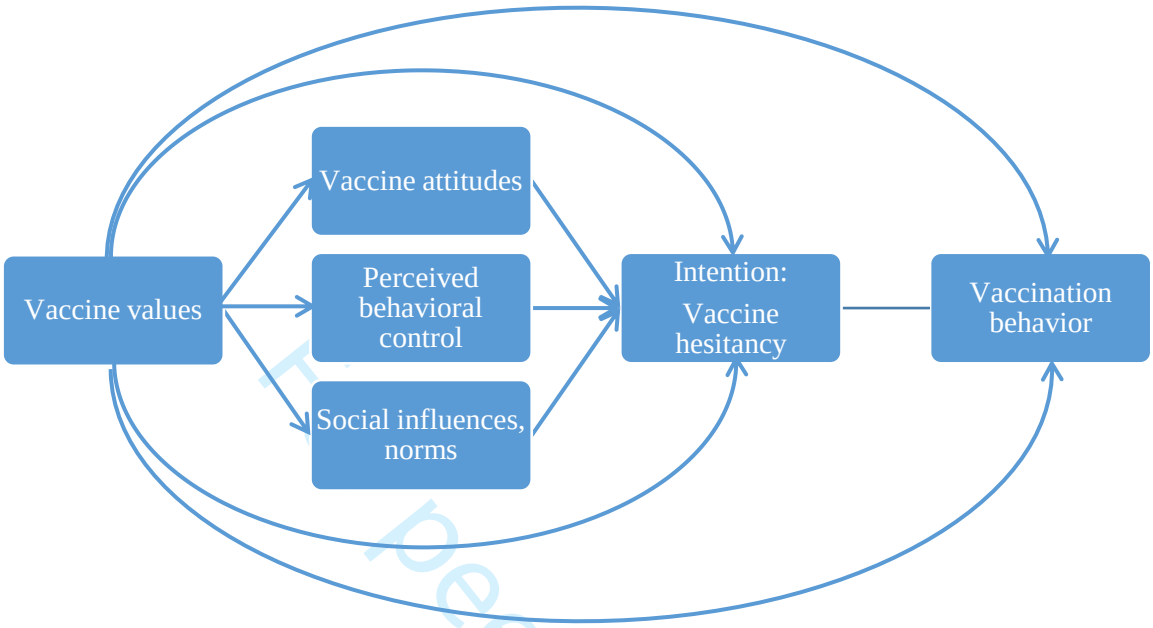
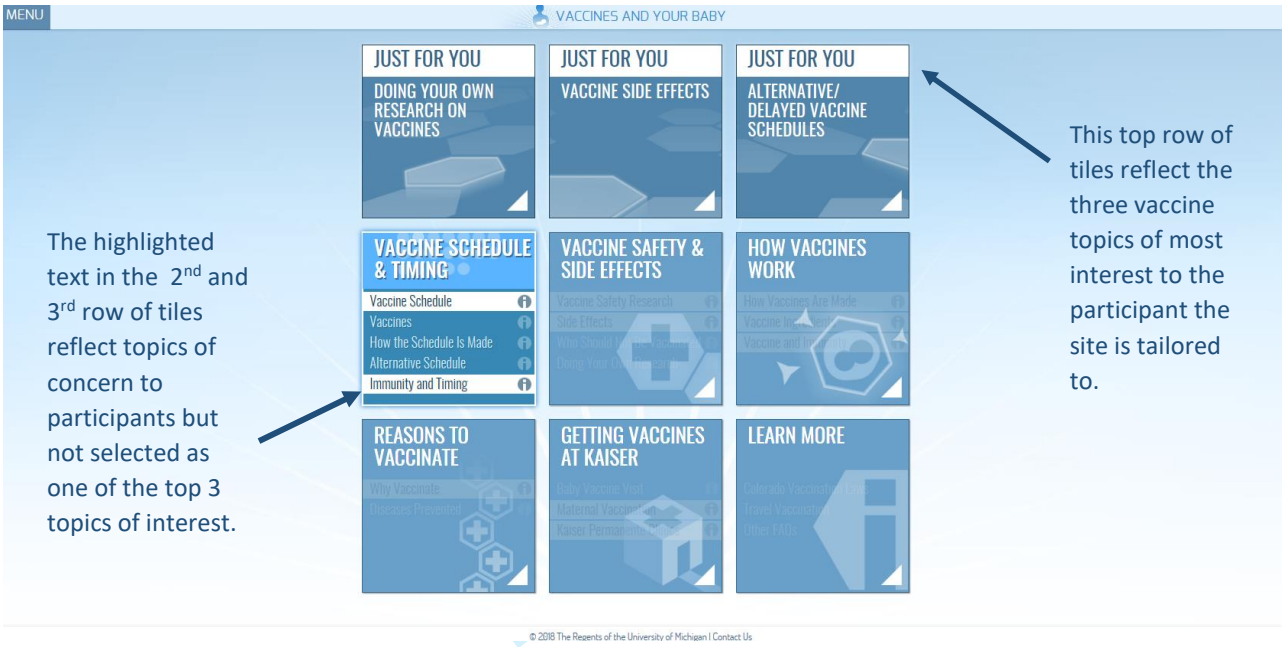


Figure 2: Screenshots of the Tailored and Untailored Intervention Websites

A. Tailored Website



B. Untailored Website

Figure Legend. The right arrow denotes the "Just for You" tiles that represent the most highly tailored content on the VAYB website. The left arrow denotes additional text reflecting lightly tailored material that is particularly salient to the participant based on their survey responses.

The "Reducing Delays In Vaccination" (REDIVAC) Trial: A protocol for a randomized controlled trial of a web-based, individually tailored, educational intervention to improve timeliness of infant vaccination

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 8
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	34
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 34
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	15
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11, 19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22-23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11, 23
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19, 24
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25

	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The "Reducing Delays In Vaccination" (REDIVAC) Trial: A protocol for a randomized controlled trial of a web-based, individually tailored, educational intervention to improve timeliness of infant vaccination

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The "Reducing Delays in Vaccination" (REDIVAC) Trial: A protocol for a randomized controlled trial of a web-based, individually tailored, educational intervention to improve timeliness of infant vaccination

Version 1.0, November 1, 2018

Amanda F. Dempsey[1] - Amanda.dempsey@ucdenver.edu

Nicole Wagner[2] - Nicole.M.Wagner@kp.org

Komal Narwaney[2] - Komal.J.Narwaney@kp.org

Jennifer Pyrzanowski[1] - Jennifer.pyrzanowski@ucdenver.edu

Bethany Kwan[1] - BETHANY.KWAN@UCDENVER.EDU

Courtney Kraus[2] - Courtney.Kraus@kp.org

Kathy Gleason[2] - Kathy.s.Gleason@kp.org

Kenneth Resnicow[3] - kresnic@umich.edu

Carter Sevick[1] - CARTER.SEVICK@UCDENVER.EDU

Jessica Cataldi[1] - Jessica.Cataldi@childrenscolorado.org

Sarah Brewer[1] - SARAH.BREWER@UCDENVER.EDU

Jason Glanz[2] - Jason.M.Glanz@kp.org

Affiliations:

[1] Adult and Child Consortium for Outcomes Research and Delivery Science (ACCORDS), University of Colorado Denver, Aurora, CO

[2] Kaiser Permanente Colorado, Institute for Health Research, Denver CO

[3] School of Public Health, Division of Health Behavior and Health Education, University of Michigan, Ann Arbor, MI

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Abstract

Introduction:

Increasing numbers of children are failing to receive many recommended vaccines, which has led to significant outbreaks of vaccine preventable diseases in the US and worldwide. A major driver of undervaccination is parental vaccine hesitance. Prior research demonstrates that mothers are the primary decision maker for infant vaccination, and that their vaccination attitudes form primarily during pregnancy and early in their infant's life.

Methods and Analysis:

This manuscript describes the protocol for an ongoing 3-armed, randomized controlled trial done at Kaiser Permanente Colorado. The trial aims to test the efficacy of provided tailored, individualized information via the internet to pregnant and new mothers versus untailored information versus usual care on the timeliness of infant vaccination. The primary outcome to be assessed is vaccination status, which is a dichotomous outcome (up to date versus not) assessed at 200 days of age, reflecting the time when infants should have completed the first set of vaccine provided (at age 2, 4 and 6 months). Infants with one or more age-appropriate recommended vaccines at least 30 days delayed are categorized as not up to date whereas all other infants are considered up to date. Secondary outcomes include vaccination status at 489 days, reflecting receive of recommended vaccines at 12-15 months of age, as well as vaccination attitudes, hesitancy and intention. Vaccination data will be derived from the

electronic medical record and the state immunization registry. Other secondary outcomes will be assessed by online surveys.

Ethics and Dissemination:

The study activities were approved by the Institutional Review Boards of the University of Colorado, Kaiser Permanente Colorado, and the University of Michigan. Results will be disseminated through peer reviewed manuscripts and conference presentations.

Article Summary:

Strengths and Limitations of the Study:

- **Strength:** Randomized, controlled trial design
- **Strength:** Population based sample
- **Strength:** Longitudinal analysis of EMR data
- **Limitation:** Only one geographic area limits generalizability

Trial Registration: This trial has been registered at ClinicalTrials.gov - NCT02665013.

Key words: vaccine hesitancy; immunization; mothers; clinical trial

Introduction

Vaccination has been touted as one of the most effective public health interventions ever created.[1] Despite this, increasing numbers of parents choose to delay or forgo recommended vaccines for their children because of uncertainty about the vaccines' safety and necessity and general mistrust of the pharmaceutical industry.[2,3] With this, increasing numbers of children are failing to receive many recommended vaccines, which has led to significant outbreaks of vaccine preventable diseases in the US and worldwide.[4,5]

Developing and evaluating interventions to counteract parental vaccine hesitancy and childhood under-vaccination is a public health priority.[6] While many prior interventions have been tested, the majority have not been effective.[7-9] Addressing vaccine hesitancy can be difficult and time consuming because parents' vaccination decisions are often complex as they are heavily influenced by emotion, past experiences, and peers.[10-12] Addressing this complexity can be difficult for health care providers who attempt to persuade parents to vaccinate their children,[13] given that typical pediatric clinical encounters last only 15 to 20 minutes. As a result, even when parents only have a few questions that might be easily answered, a provider may feel "burnt out" when having to discuss vaccines with questioning parents.[14] In addition, in many cases the resistance to vaccination is related to psychosocial and political beliefs as much, or even more than, knowledge deficits.

Given this, new approaches to address vaccine hesitancy that are time efficient and address the complex factors influencing vaccine decision-making are needed.[15] One promising approach is

to use message tailoring to provide parents with information about vaccines that is customized to their own personal needs *before* their child's clinical appointments. Message tailoring allows for written information to be individualized to reflect each person's unique beliefs, experiences, knowledge, attitudes, and barriers to action.[16] By doing so, the personal relevance of the information increases which in turn improves individuals' receptiveness to that information – this is especially important in the case of vaccine hesitancy when the new information may not align with a person's current attitudes or beliefs.[16] This approach has been shown to be effective for improving compliance with a number of health behaviors but only minimally applied to vaccination. [17,18]

This manuscript describes the protocol for a 3-armed randomized controlled trial testing the effectiveness of a web-based tailored messaging intervention called "Vaccines and Your Baby" (VAYB) versus an untailored version of the intervention versus usual care for improving timely uptake of recommended childhood vaccines.

Conceptual Model

The conceptual model for the intervention is based on a hybrid of the theory of planned behavior (TPB) and the value-attitude-behavior hierarchy model (Figure 1).[19,20] It also incorporates strategies derived from motivational interviewing and self-affirmation.[21,22] According to the TPB, behavior (in this case, following the recommended vaccination schedule) is influenced by intentions (in this case, vaccine hesitancy), which are a result of attitudes towards the behavior, perceived behavioral control, and norms. This intervention primarily

focuses on strategies for influencing attitudes – i.e., tailored messages addressing individual behavioral beliefs (e.g., beliefs that immunity is best achieved through exposure to a pathogen, or "natural immunity") framed according to personal values (e.g., emphasizing the benefits of vaccination for preventing spread of illness among the young and elderly for those who value protecting one's community). By affirming individual patient values and identity, using non-judgmental and empathetic language, emphasizing autonomy (i.e. adding tenets from Motivational interviewing and Self Determination Theory)[21,23,24] and constructing controlling tones of messages, this can minimize reactance and counterarguments. Individually tailored messages in general are known to have greater effects on attitude change than are universal (untailored) messages.[20,25,26] According to the value-attitude-behavior hierarchy model[27], values influence attitudes and behavior across cultures and domains, including recycling, consumer behavior, and alcohol consumption.[28,29] This hybrid approach to establishing the conceptual model allows us to focus the intervention strategies on addressing a select set of known determinants of vaccine hesitancy and behavior, rather than incorporating the universe of behavior change techniques into our intervention.

Aim and Hypothesis

The primary aim of this study is to conduct a three-group randomized, intervention trial to measure the effectiveness of the VAYB intervention versus a similarly constructed but untailored intervention versus usual care on vaccination receipt and timeliness during an infant's first 15 months of life. Our intervention approach (the VAYB intervention) is novel in that it combines values framing with message tailoring for vaccination to change parents'

attitudes and behavior. The primary hypothesis to be tested is that infants of mothers who receive values-framed, individually tailored messages (e.g. the VAYB intervention) will have lower levels of vaccine hesitancy and more up to date vaccination behavior than those receiving an untailored version of the intervention or those receiving usual care. A secondary aim of the project is to assess the impact of the intervention on vaccination attitudes and hesitancy level, particularly as these relate to our conceptual model described above.

Methods

A summary of the trial's specifications is shown in Table 1.

Study Design and Registration

This is a 3-armed, individually randomized clinical trial with longitudinal follow up. Study arms include 1) the VAYB (tailored) intervention, 2) an untailored version of the intervention and 3) usual care. The study is registered with ClinicalTrials.gov (NCT02665013, see Table 1 for details).

Study Overview and Setting

In the trial, participants are active in the study from the time of enrollment (from late pregnancy or the first two months of their infant's life) until their infant reaches 15 months of age (489 days). The primary vaccination outcome to be assessed is a dichotomous outcome of vaccination status (up-to-date versus not) that is based on the average number of days under

vaccinated for all vaccinations in the recommended vaccine schedule. Assessment of vaccination for the 2- and 4-month vaccines occurs when the infant is 200 days old (to provide additional time beyond the exact date the vaccine was due). Secondary vaccination outcomes and outcomes related to attitudes and hesitancy are assessed at 489 days of age. This time period was chosen to encompass three critical decision making points associated with the vaccination process; 1) during pregnancy when many vaccination decisions and attitudes are being formed;[30,31] 2) during the time period that corresponds to the ages when the initial infant series is recommended (generally at ages 2, 4 and 6 months); and 3) during the second stage of the infant vaccination series at age 12-15 months when vaccines different from those offered at the initial stage are introduced. The primary outcome (vaccination behavior) is assessed using data from the electronic medical record, augmented with data from the Colorado immunization registry, CIIS.

The study takes place via the internet. Participants in the VAYB and untailored arms view educational materials on a web-enabled device or computer of their own and are prompted to view this information again at specific time points during the study (described below). Participants enrolled in the usual care arm receive by mail Vaccine Information Statements (VIS) for all recommended vaccines in the child's first year of life; VISs are not provided by mail to participants in the VAYB or untailored arms. Participants in all arms complete surveys at baseline, and three additional time points (Table 2). Participants are reminded to take the survey at these intervals via a series of emails. Following survey completion, participants are taken automatically to the website that contains either tailored or untailored information,

depending on study arm. The infants of participants in all arms receive care at participating clinics (an eligibility criterion, see below) where VISs are provided to all study groups as part of routine care.

Study Population and Inclusion/Exclusion Criteria

Women in the third trimester of pregnancy enrolled at Kaiser Permanente Colorado (KPCO) between April 2016 and October 2017 are recruited for the trial. KPCO is a nonprofit, managed care organization serving ~667,000 individuals. Each year ~5,000 pregnant women and 140,000 children receive health care at KPCO clinics. Study participants can enroll from the first recruitment outreach that occurs in the last trimester of pregnancy to when their infant is $\leq$ 2 months of age. The infant must be enrolled in the KPCO health plan to continue participation in the study.

A combination of electronic medical record (EMR) data and study screening questions are used to determine study eligibility. First, the EMR is used to identify English speaking women, currently enrolled at KPCO, and $\geq$ 18 years of age in the last trimester of pregnancy, based on clinically determined expected delivery date. All identified women with a diagnosis (ICD10) code in the past 8 months indicating potential abortion, miscarriage, adoption, fetal anomalies, or genetic disorders in the pregnancy, or a high risk maternal condition (i.e. cancer) are flagged for potential exclusion. Medical chart reviews are conducted on these women and they are definitively excluded as potential participants if the EMR indicates their fetus has a high-risk

condition (e.g., fatal heart condition, trisomy 18, anencephaly), or they have a spontaneous or elective abortion, social issues (such as domestic violence), or serious health concerns. Screening questions are delivered online before consent to ensure participants plan to use KPCO medical care for their child, are ≥ 18 years of age, and are currently pregnant or have a child less than 2 months of age. During the course of the study, participants are removed if they have a fetal demise, infant death, if the infant loses KPCO insurance coverage for greater than 90 days, if they request to be removed from the study or if they die. This data is obtained from a monthly data extraction from the EMR and patient report.

Consent and Recruitment

Recruitment occurs via a multistep process. After the EMR is used to screen for initial eligibility, a series of 2 letters, 3 emails, and one phone call are sent to potential participants 1-2 weeks apart to direct patients to the KPCO study registration website created specifically for this study. On this registration website identity and eligibility are confirmed, and the participant is consented by signing an online form.

After consent participants are directed to the *study* website where they set up login information and are provided with a Pre-intervention Questionnaire that assesses their baseline intention to vaccinate, vaccination values, logistical barriers to vaccination, vaccine hesitancy (used for randomization), and demographics, and re-confirms eligibility. Previously developed and validated measures are used to assess these items.[32-34] Upon completion of this

questionnaire, participants are considered to be “enrolled” in the study and are randomized (described below). The screening, consent and enrollment process is repeated monthly until the target sample size is reached.

Assignment of Interventions

Participants are randomized on a 1:1:1 basis between the VAYB, untailored and usual care arms. The allocation assignment is generated by back-end software embedded in the study website. Randomization occurs immediately following enrollment into the study (i.e. after completion of the pre-intervention questionnaire) and remains in place throughout the study. Stratified randomization along with a permuted block technique is used such that participants are first stratified into either a hesitant or non-hesitant group, based on responses to the pre-intervention questionnaire. Hesitancy status is assessed using a 5-item validated measure developed by (Opel, personal communication) and participants are categorized based on the measure’s suggested (but unpublished) cutoffs. Participants from each group are then added to their own set of blocks that each contain 6. There are 2 slots available for each of the 3 study arms. These slots are randomly ordered when the block is created. When all 6 slots are filled, a new block with 6 randomly ordered slots is added.

Blinding

Participants are not informed about which study arm they are assigned to, but descriptions of the three potential arms for assignment are provided in the study consent documents. Thus, although they are not told specifically which arm they are in, they are not blinded to their study assignment. The project manager for the study will convert study data to unlabeled arms (i.e. arm 1, 2 or 3) allowing for the rest of the study team to be blinded to study arm assignment during the analysis and data interpretation phases of the project. Unblinding will occur when data analysis is complete for the primary study outcome. Clinics where participants receive care are not aware of the individuals participating in the study unless brought up by the patient during a clinical encounter.

Sample Size Calculation

We considered, based on prior studies,[3,35] an odds ratio (OR) between 2.0 and 3.0 for up-to-date vaccination status between the intervention study arms and usual care to be clinically meaningful. For this, we estimate a needed sample size of 477 (OR = 3.0) to 1002 (OR=2.0) participants. This sample size is based on an assumption of 15% of the recruited population being vaccine hesitant (as has been the case in prior studies in this population)[35] and therefore not up to date in their infant's vaccination, a 1:1:1 randomization allocation ratio, two-sided tests of statistical significance, 80% statistical power, and a 5% type I error rate. Accounting for an attrition of 15%, we need to enroll 561 to 1179 participants.

Interventions

Tailored Intervention

In the VAYB arm messages were tailored for multiple constructs including intention to vaccinate, personal attitudes about vaccines, vaccination values (Table 2), vaccination beliefs and concerns, logistical barriers to vaccination, and child's name, sex and birthday. Data to inform this initial tailoring come from the Pre-Intervention Questionnaire. Interim questionnaires are used to refresh the tailored information at 3 times during the study period. Tailoring occurs based on an embedded algorithm that is part of the VAYB website. An in-depth description of the process used to develop the VAYB intervention, and the resulting content, is described in detail elsewhere but examples are provided in Table 3.[33,34]

Upon completion of the pre-intervention questionnaire where initial tailoring information is obtained, participants are automatically directed to the VAYB website which is individually customized based on their responses. The most highly tailored content is in three "Just for You" tiles that are displayed prominently on the page (Figure 2A). These tiles reflect the top three vaccine topics of concern that each participant indicates they want more information about and are further customized to highlight the vaccination values the participant most endorses, and to reflect their most recently reported intention to vaccinate. The remaining content is lightly tailored to reflect participant's attitudes, concerns, hesitancy and demographics, but is not tailored based on vaccination values. Highlighted text on the home page (Figure 2A) is used to further identify additional information that is most relevant to the participant based on their survey answers. The website is refreshed 3 times during the course

of the study based on interim assessments of participants' attitudes, beliefs, concerns, values and vaccine hesitancy. Specifically, when the infant is 4 to 6 months of age, participants re-answer all questions excluding the value items and questions used to assess vaccine hesitancy, and the content is refreshed accordingly. Values are reassessed again in a 3rd survey when the infant is 10 to 12 months and the website is refreshed to reflect any new content. Vaccine hesitancy level is reassessed at a 4th survey and the content is again refreshed. Participants receive a gift card after each survey is completed. For all time points, vaccination intention is assessed immediately before and within the hour after viewing the website content (VAYB and untailored arms). A reminder for this vaccination intention assessment is sent to non-responders after one day.

Untailored Intervention

To isolate the impact that message tailoring has on mothers' vaccination attitudes and behavior, the primary comparator group in the study is a website that is similarly constructed as the VAYB website but lacks tailored elements. Specifically, the untailored intervention has similar text, content and design as the VAYB intervention, but is not linked to survey responses to make the messages individually customized (Figure 2B). This means that each participant in this arm receives identical content, messages, text and images. For example, instead of name-tailoring, the text uses generic references such as "you" and "your child". The recommended vaccine schedule is static in the untailored site compared to the tailored site which highlights upcoming vaccines based on the child's age. The order of content displayed is fixed throughout the study period as there is no linkage of the website's text to participants' values or attitudes.

In addition, the highly tailored "Just for You" tiles are not present in the untailored intervention. The same questionnaires administered to participants in the VAYB arm are administered to participants in the untailored arm, but the material is not used to refresh the website content

Usual Care

After taking the Pre-Intervention Questionnaire that is used to determine randomization, participants in the usual care arm are thanked for their information and logged off the study website. They receive an email containing their gift card and are mailed the Vaccine Information Statements for the vaccines due in the child's first year of life. They do not have access to the VAYB or untailored websites used for the other arms of the study but do receive the same interim questionnaires at the same time periods as the VAYB and untailored arms (see Table 2). They continue their usual care and their infant's vaccination status is assessed prospectively when their child turns 200 days old (primary outcome) and again when their child is age 489 days (secondary outcome).

Routine pediatric care is available to infants of all participants in the study. At KPCO, usual care typically consists of a series of pediatric, well-child care visits at 2 weeks, 2 months, 4 months, 6 months, and 12 months of age, with an optional visit at 9 months of age if desired by the healthcare provider or parent. Visit content is structured based on the Bright Futures program of American Academy of Pediatrics, which provides detailed guidelines regarding the content and schedule of pediatric health supervision visits.[36] The visit content is intentionally broad,

with visits focused on the needs of the child and family that typically last 20 minutes or less. Based on data in the EHR, a pre-visit informational sheet lists the vaccines recommended at that visit. Parents are also provided with the VISs relevant to that visit. Providers are often asked about vaccination, and can provide additional information verbally, although the small window of time available for visits can limit discussion.

Outcomes

The primary outcome of the study is a dichotomous categorization of vaccination status (up-to-date vs. not up-to-date) that is defined based on a continuous measure of days under-vaccinated. This outcome is assessed at 200 days of age to cover vaccines in the initial infant vaccination series and to minimize the loss to follow-up. The following 6 vaccines recommended by the Advisory Committee on Immunization Practices will be assessed: hepatitis B; rotavirus; diphtheria-tetanus-acellular pertussis; Haemophilus influenzae type b; pneumococcal conjugate vaccine; and polio. All vaccination data is obtained from KPCO's EMR CIIS.

To categorize vaccination status we will first assess the number of days under-vaccinated for the 2- and 4-month vaccines (combined), by calculating the difference between when a vaccine dose was actually administered and when a vaccine dose should have been administered according to the vaccination schedule recommended by the Advisory Committee on Immunization Practices,[37] plus an additional 30 day "leeway" to account for vaccination that did

not occur at exactly the minimal interval between doses. For example, the first dose of rotavirus vaccine is due at age 2 months (61 days) but is not considered late until age 92 days. Days undervaccinated for this dose begin accruing on day 93. The number of days under-vaccinated is then summed across all doses and vaccines to calculate a total number of days under-vaccinated for each infant and can range from 0-648 days. Infants with 0 total days undervaccinated (assessed specifically for the 2 and 4 months vaccines) at 200 days will be considered up-to-date on their vaccination status; Those with ≥1 days undervaccinated (representing at least a 30-day delay for at least 1 vaccine) will be considered not up-to-date.

A secondary vaccination metric that is assessed is up-to-date status for measles-mumps-rubella (MMR) and varicella vaccine at 489 days, when delay for the first dose of these vaccines begins. This metric is useful because it incorporates outcomes related to parents' decision-making about these two vaccines recommended at 12-15 months of age that are not offered previously.

The interventions' impact over time on a variety of additional secondary outcomes that are based on the constructs of our conceptual behavioral model (Figure 1) and assessed as part of the baseline and interim questionnaires will also be assessed. These include changes over time in vaccination attitudes and hesitancy, and how these relate to study arm, vaccination values, and vaccination status. Vaccination attitudes are assessed using measures previously developed by our team and others,[32] values are assessed using a novel vaccination values framework we have developed (manuscript in preparation), and vaccine hesitancy is assessed using a 5-item

validated measure developed by (Opel, personal communication). A variety of covariates and potential moderators will be assessed as part of this analysis including patient age, gender and insurance (some patients have Medicaid KPCO coverage), and mother's age, race, and ethnicity. Also included will be metrics measuring website engagement (VAYB and Untailored arms only) including time spent on the website, number of times viewing website, number and order of pages viewed, and match between stated concerns and website material viewed (VAYB arm only).

Data Collection Methods

Vaccination data is collected routinely as part of clinical care within the KPCO health system and will be assessed from the KPCO EMR data warehouse at pre-defined ages (200 days and 489 days). CIIS will be used as a secondary vaccination data source, though internal audits demonstrate that >95% of childhood vaccines given to KPCO patients are captured within the EMR. Survey data are collected on the internet based on user responses to the online questionnaires.

Participant retention

To assist with retention, participants receive a $20 gift card incentive for each survey they complete. However, even with this incentive we expect some drop off in survey participation. Because our primary outcome is vaccination status, mothers who do not participate in all the study surveys are still able to have the primary study outcome assessed, so long as their child

maintains coverage and continues to seek care within the KPCO health system. Based on past studies, we expect that the proportion of mothers who discontinue KPCO coverage after the birth of their infant to be ~15%, and our study is powered with this attrition in mind.[35]

Data security and storage

To ensure that the data are protected, several methods are used. Personal identifying data collected on study websites is limited to a participant generated username, email address, and child birthdate. The only other data collected on the study websites are vaccine attitudes, beliefs, values and demographics. The study websites use virtualized servers housed at redundant data centers and access is password protected. Virtual servers are backed up automatically onto encrypted tape for recovery and security. Data provided to researchers from the website are encrypted if they are transmitted across the Internet. Data use agreements are in place across all study team member sites.

All medical record data are collected and stored at KPCO behind the firewall in secure password protected files. This dataset is linked to a study ID. A limited dataset devoid of personal identifying information will be used for data analyses. Data will be shared with study team members through a secure file transfer. Only members of KPCO research project team have access to the personal identifiers linking the study IDs to specific study participants.

Statistical Methods

Total days undervaccinated will be analyzed primarily as a dichotomous variable (up-to-date vaccination status) and secondarily as a continuous measure. Categorically defined up-to-date vaccination status will be analyzed using logistic regression to estimate odds ratios and associated 95% confidence intervals. For the continuous measure, because total days undervaccinated has a highly skewed distribution, we will use a nonparametric analysis and a rank transformation approach. For both measures, we will conduct analyses stratified by baseline vaccine hesitancy.

For survey measures, descriptive statistics will be assessed and changes in vaccination attitudes and intention over time will be calculated. All measures are assessed using Likert scales and will be analyzed as linear measures. Repeated measures ANOVA will be used to assess the intervention's impact on average change by arm for each of these outcomes. Mixed linear models will be used to assess the "difference in difference" over time in these means, by arm, controlling for the covariates described above. Website utilization data will be measured primarily using linear measures (time spent on the website in minutes, number of times logging in, number of web pages viewed etc.) and may be included in the mixed linear models. ANOVA will be used to assess the association between each of these website utilization measures and study arm.

Analytic framework

We will use a modified intention to treat framework for the analysis of vaccination outcomes. This analytic cohort will include infants of all randomized mothers who maintained KPCO health coverage for the allotted amount of time (200 days for the primary outcome, 489 days for the secondary outcome) with no more than 90 days of no coverage, and thus have vaccination data available for assessment. For survey outcomes, we will use a modified intention to treat analysis that includes all participants with data from at least one non-baseline questionnaire.

Missing data

As described above, nearly all vaccines provided to KPCO patients are documented in the EMR, and doses provided outside KPCO are documented in CIIS. Therefore, we expect there to be minimal missing data for vaccination outcomes. To ensure the most complete record, CIIS will be cross checked for all participants to identify any vaccine doses given to infants outside the KPCO system that are missing from the KPCO EMR. Participants who do not have vaccination data present in either system will be assumed to have not gotten a vaccine dose elsewhere.

For survey data, due to our recruitment strategy, we anticipate no missing data at baseline, as completion of the baseline survey was a criterion for entry into the study. However, there may be missing data for subsequent surveys as these were not required to remain in the study. For missing data in surveys beyond baseline, multiple imputation models will be developed for

analyses involving multiple survey points where greater than 10% of subjects would be lost due to missing values.

Subgroup analyses

The main subgroup analysis planned is examining the efficacy of our intervention by vaccine hesitancy status (dichotomous variable), as defined by the 5 item Opel measure described above.

Monitoring

KPCO EMR data on participants and their infants will be used to identify any deaths or loss of KPO insurance coverage, which are subsequently chart reviewed for accuracy. Participants who die or experienced an infant death, or have >90 days loss of insurance coverage, will be removed from the study and will not be included in the modified intention to treat analysis. All participants will be monitored weekly for completion of the various surveys in the study and reminder emails will be sent on a pre-set schedule to those who have not completed them. However, failure to complete any surveys beyond the baseline survey will not be cause for removal from the study.

Assessment of Harms and AEs

Study participants are provided with contact information for the research team and encouraged to contact the team if they experience any adverse events related to their participation in the study (e.g. being contacted after an infant death). Adverse events are expected to be very unlikely given the nature of the study and our monitoring procedures. However, should any significant adverse events occur, they will be reported to the appropriate institutional authorities.

Ethics and Dissemination

Approvals

This study is approved by the Institutional Review Boards at the University of Colorado, and KPCO.

Informed consent

All mothers in the study are informed about the study, the risks and benefits and provide written informed consent via an on-line registration process prior to participating in the study. As part of the consent process participants are informed that they may withdraw from the study at any time without impacting their clinical treatment.

Access to data

The data will be accessed only by authorized persons directly involved in the study from the University of Colorado Denver, KPCO and University of Michigan. Access to a de-identified, aggregated version of the dataset and analysis code will be available upon request and approval of the study team

Competing Financial Interests

Amanda Dempsey serves on advisory boards for Merck, Pfizer, and Sanofi and as a consultant for Pfizer. She does not receive any research funding from these companies and they played no role in this project. All other research team members have no competing financial interests to declare.

Dissemination Plans

Results of the study will be presented at national and international research conferences and through peer-reviewed publications. Any changes to the study protocol will be clearly communicated to journals publishing the study results in a manner that aligns with the journal's policies for reporting clinical trials. CONSORT guidelines[38] will be followed when reporting study outcomes. Study materials such as questionnaires and screenshots of the intervention websites will be available to researchers upon request from the study Principal Investigators. If the VAYB intervention proves to be efficacious in reducing delays in the timeliness of infant

vaccination, the study team will work with web-developers and community organizations to explore options to make the website available to the general public.

Patient and Public Involvement

Patients were first involved in this research when designing the intervention, which is informed by the literature, and by the research teams prior clinical and research experience. The bulk of patient involvement was as research participants. They will not be involved in recruitment or conduct of the study, data analysis, or dissemination.

Figure Legends

Figure 2: The right arrow denotes the "Just for You" tiles that represent the most highly tailored content on the VAYB website. The left arrow denotes additional text reflecting lightly tailored material that is particularly salient to the participant based on their survey responses.

Table 1. Trial Registration Dataset Summary Table

Data Category	Information
Registry and trial number	ClinicalTrials.gov - NCT02665013
Data of registration	1/4/2016
Secondary identifying numbers	CO-IRB #: CO-15-2299_07
Financial Support	National Institutes of Health
Contact for queries	Amanda.dempsey@ucdenver.edu
Title	The REDIVAC study-Reducing Delay in the Vaccination of Children
Countries of Recruitment	United States
Health condition studied	Infant vaccination
Interventions	Active comparator – tailored educational website Placebo comparator – untailored educational website Passive comparator – usual care
Key inclusion and exclusion criteria	Inclusion: ≥18 years, pregnant in 3rd trimester or child <2 months of age, receives care at KPCO health system, able to read English, access to the internet. Exclusion: high risk maternal or fetal health condition, maternal social issues (such as abuse), fetal or infant death, does not plan to have infant receive care in KPCO health system after birth

Study type	Individually randomized, controlled trial
Date of first enrollment	4/20/2016
Target sample size	700
Trial status	Ongoing data collection
Primary outcomes	Average days undervaccinated; Up to date vaccination status
Key Secondary Outcomes	Vaccination attitudes; Vaccination values; Vaccine hesitancy level

Table 2. Timing and Content of Study Questionnaires

Timing	Rationale	Content
Last trimester of pregnancy or child <2 months of age	Pre-intervention questionnaire required for study enrollment. Our prior research indicates infant vaccination decisions are actively forming among expectant mothers.	Intention to vaccinate Vaccination values Vaccination attitudes Logistical barriers Vaccine hesitancy status Demographics
At child age 4 to 6 months	First round of infant vaccines is typically provided at age 2, 4 and 6 months. The same vaccines are given at each visit.	Intention to vaccinate Vaccination attitudes Logistical barriers Vaccine hesitancy (only 3 of 5 Qs)
At child age 10 – 12 months	The same vaccines are provided at 2, 4 and 6 months of age, thus decisions made at the two-month visit are likely to be followed for 4 and 6-month vaccines. However, several new vaccines are introduced at the 1-year visit. Vaccine-hesitant parents are	Intention to vaccinate Vaccination values Vaccination attitudes Logistical barriers Vaccine hesitancy status

	likely to need additional, new information for making decisions about the vaccines provided at age 1 year.	
Age 13-15 months	End of study assessment to track changes over crucial time periods of vaccine decision-making	Vaccination attitudes Vaccine hesitancy status Satisfaction with website

Table 3 Examples of VAYB Website Content for Two Topics, Showing Tailoring Based on Three Different Values

Vaccines and Your Baby: Tailored Messages		
Value	**Topics**	
	"Alternative /Delayed Vaccine Schedules" Message	**"Doing your own Research on Vaccines" Message**
Security – Disease Prevention	Like many parents, your main goal is to keep your child healthy. The last thing you want is for your child to get an illness you could have prevented with a simple vaccine.	You're the kind of person who will do everything she can to protect her baby from illnesses.
Self-Direction	You're not one to just do what other people tell you to do. You know your child better than anyone, and you have choices to make. You want to do your own research about vaccines. You don't want him/her to get a disease. But you don't want to put him/her at risk by getting vaccines.	You're the kind of person who plays an active role in decisions about her baby's health.
Security – Vaccine Risk	That's a lot of needles (and a lot of tears)! You want to protect your child. But with so many vaccines at once, you're concerned about exposing him/her to too many unnatural ingredients all at once.	You're the kind of person who will do everything she can to protect her baby from pain or unnecessary medicines.

Author Statement.

Amanda Dempsey conceived of the study and intervention, and wrote the first draft of the manuscript.t.

Nicole Wagner provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Komal Narwaney provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Jennifer Pyrzanowski provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Bethany M Kwan provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Courtney Kraus provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Kathy Gleason provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Ken Resincow provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

carter sevick provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Jessica Cataldi provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Sarah E Brewer provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

Jason M Glanz provided input into the study design, intervention development, and study protocol, and edited versions of the manuscript.

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Competing Interests:

Amanda Dempsey serves on Advisory Boards for Merck, Pfizer and Sanofi Pasteur, and has provided consulting services to Pfizer. She does not receive any research funding from these companies. All other authors have no competing interests to declare.

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FIGURE LEGENDS

Figure 1: Model of parental vaccine values, vaccine attitudes, hesitancy and behavior

Figure 2. (a) "Landing page" of the VYB website annotated to highlight various types of message tailoring. The right arrow denotes the "Just for You" tiles that represent the most highly tailored content on the VAYB website. The left arrow denotes additional text reflecting lightly tailored material that is particularly salient to the participant based on their survey responses.. (b) Landing page of corresponding untailored website that lacks message tailoring

Figure 1: Model of parental vaccine values, vaccine attitudes, hesitancy and behavior

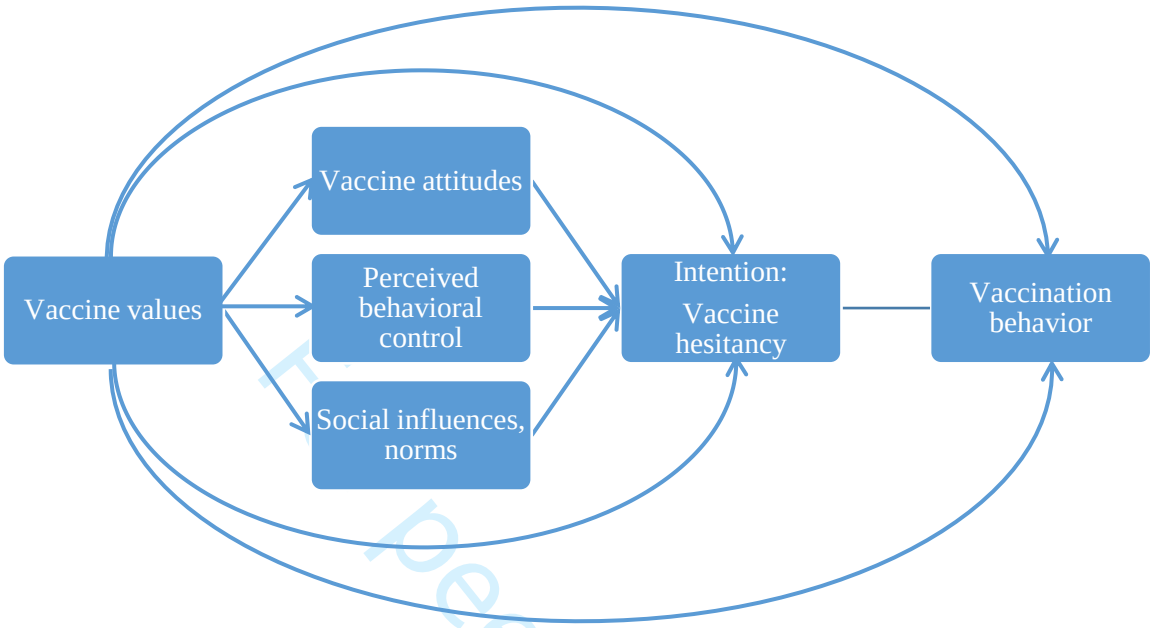

Figure 2: Screenshots of the Tailored and Untailored Intervention Websites

A. Tailored Website

B. Untailored Website

The "Reducing Delays In Vaccination" (REDIVAC) Trial: A protocol for a randomized controlled trial of a web-based, individually tailored, educational intervention to improve timeliness of infant vaccination

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 8
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	34
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 34
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	15
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11, 19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22-23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11, 23
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19, 24
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25

	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.