Reducing Health Disparities in Unintended Pregnancies Among Hispanic Adolescents Using a Patient-Centered Mobile Health Application, Health-E You/Salud iTu

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

University of California, San Francisco

July 31, 2019

NCT02847858

Study Overview

A cluster randomized controlled trial of 18 school based health centers (SBHCs) with 1,360 Latina adolescents evaluated the extent to which the app: (1) supports adolescents in making decisions about an effective method of contraception; (2) improves the effectiveness and efficiency of the clinical encounter; and (3) reduces the incidence of unprotected sexual intercourse among Latina adolescent girls over time. The long term goal of the intervention is to reduce health disparities in unintended pregnancy rates for Latina adolescents. Clinics provided all adolescent girls with an iPad. The iPad assessed eligibility and obtained consent. Participants in the nine intervention clinics received the app and those from nine control clinics received standard of care sexual health questions. In addition to the baseline, pre-visit questionnaire, participants were asked to complete follow-up surveys within 48-hours, 3 and 6 months after the visit. Differences in adolescents' contraceptive knowledge, attitudes, self-efficacy and use over the 6-month follow up was assessed by generalized mixed effects models that to account for repeated measures, a time effect, the time by group interaction, and demographic covariates.

Study Setting

Our study took place in Los Angeles County which holds the second largest school district in the United States. It is an ideal setting to conduct this cluster randomized control trial as it has a large number of SBHCs, serves a large proportion of Latina adolescents and has high rates of unintended pregnancies and sexually transmitted infections (STIs) (reflecting unprotected sex). [i,ii] In addition, these sites expressed a willingness and commitment to participating in a rigorous, randomized control trial.

Participants

Participant recruitment began in August 2016 and continued through May 2018. All adolescent girls ages 14- 18 years who visited any of the participating SBHCs, regardless of reason for visit, were invited to use an iPad with the web application. The computer assessed eligibility of the teens using an online screener built in to the app. The inclusions criteria for the study is outlined below.

Inclusion criteria

Adolescents were eligible to participate in the study if they met the following criteria:

- Female
- Aged 14–18 years
- Hispanic/Latina
- Had an appointment at a participating SBHC
- English-speaking or Spanish-speaking

- Sexually active (have had sexual intercourse)
- Not currently pregnant or not sure that they are pregnant (adolescents with a previous pregnancy and who are not currently pregnant were eligible)
- Not using an LARC method of contraception at the time of the screening.

Exclusion criteria

Adolescents were not eligible to participate in the study if they were:

- Not biologically female
- 13 years or younger or 19 years or older
- Did not identify as Hispanic/ Latina
- Used the app outside of a participating SBHC appointment
- Not sexually active
- Pregnant at the time of screening
- Using a LARC method of contraception at the time of screening
- Did not complete the intervention or baseline questionnaire

SBHCs were randomly assigned, at equal chance, to either the intervention (*Health-E You/Salud iTu* app) or control group (standard of care, no app). This design allows our analyses to isolate the effect of the app and determine whether the app increases adolescent sexual health and contraceptive knowledge, self-efficacy in selecting an effective method, satisfaction with the visit and contraceptive use and adherence over time.

Clinics were randomized to either control or intervention group using computer-generated random number assignment. Following randomization, our local partners from The Los Angeles Trust for Children's Health (LA Trust) notified the SBHCs of their assignment and provided the necessary training around the study aims, use of the iPad and integration into the unique workflow at each SBHC (determined in partnership with our community outreach staff and clinic staff, providers and managers). The LA Trust also provided technical support to ensure that all sites had a reliable internet connection to be able to use the app as intended and to securely transmit data gathered from the app to the University of California, San Francisco (UCSF).

Study Outcomes

The outcomes for this study were developed in collaboration with our community, clinic and adolescent partners to address three main questions:

1) How well does the patient-centered, interactive, individually tailored *Health-E You* app engage and support Latina adolescents in understanding their risk of an unintended pregnancy and in making decisions in selecting among effective contraceptive options that can reduce their risk?
2) To what extent does the app improve adolescents' and clinicians' perception of the quality and efficiency of the visit?
3) How well does the app improve, sexually active Latina adolescents use of and adherence to effective contraceptives over time?

From these questions, we developed the specific study aims and corresponding outcome measures. The following is a description of each outcome measure for each study aim, the type of outcome (primary or secondary), the rationale for the outcome measure and the purpose for the measure.

Aim 1: Examine the extent to which the Health-E You contraceptive app supports adolescents in making decisions about an effective method of contraception.

Aim 1a) increase adolescents' knowledge of sexual health and contraceptive options

Outcome Measure: Knowledge was a secondary measure that was assessed with a 7-item scale that used a true/false format (scores range 0-7). A higher score indicates more knowledge. The items are: 1) Birth control pills do not reduce the risk of getting a sexually transmitted disease (STD); 2) As long as the male partner pulls out before he ejaculates (cums), the female will not get pregnant; 3) Weight gain is a common side effect of most birth control methods, especially for the Intra-Uterine Device (IUD); 4) Birth control pills begin working as soon as you start taking them; 5) Decreased menstrual bleeding from using IUDs does not cause health problems later on; 6) Long-acting contraception methods, like the IUD and implant, can make it more difficult to become pregnant in the future; 7) The IUD is easy for a medical provider to insert and remove.

Rationale: Knowledge is an important component of the theoretical framework of the intervention aimed to change behavior. Youth indicated that misconceptions about contraception contributed to their selecting less effective methods. Youth informed content of app and corresponding knowledge items to improve the ability of the app to address common contraception misconceptions and empower youth to be more informed about their options.

Purpose: Information provided on the app was designed to increase knowledge in these key areas via a repeated, self-administered survey immediately before and again after using the app.

Aim 1b) increase the proportion of adolescents who report being prepared to select an effective form of contraception; and

Outcome Measures: Patient Activation/Readiness was measured with the following items: "The App helped me choose a method of birth control" and "The App gave me useful information about birth control". Likert scale (options 1= strongly disagree to 5=strongly agree) which was then dichotomized into agrees versus neutral/disagrees.

Rationale: The app was designed to support adolescents in selecting a method that was a "good fit" based on their attitudes, goals, experiences and lifestyle considerations.

Purpose: To examine adolescent's perspective on the value of the app in helping them become educated about birth control and support them in choosing a contraceptive method.

Aim 1c) increase adolescents' self-efficacy to select and use an effective contraceptive method.

Outcome Measure: Contraception Use Self-efficacy. This primary outcome measure was based on a 3-item attitudinal scale to assess perceived confidence to choose and use contraception was self-administered via online survey. Each item scored on a 0-10 scale (0=not at all confident to 10=completely confident scale). Scale score is the sum of 3 items (range 0 – 30); higher score= greater self-efficacy. The questions were "How confident are you that you"…. 1) "can talk to your doctor about what birth control method(s) to use?" 2) "Can use birth control correctly so you do not get pregnant?" 3) "Have the information you need to choose the most appropriate birth control method for you?" It compares change in Intervention vs controls over time from baseline to 48-hour, 3-and 6 month follow-ups. Cronbach's alpha ranged from .74 to = .80.

Rationale: Self-efficacy is a central aspect of the theoretical model predicting behavior change for the intervention. The purpose was to assess the effect of using the app at their health care visit on the self-confidence to choose and use contraception.
Purpose: To assess the effectiveness of the app on improving contraceptive knowledge so that youth would be able to make more informed decisions when selecting a method.

Aim 2: Evaluate the efficacy of the Health-E You contraceptive app on its ability to improve the effectiveness and efficiency of the clinical encounter.

2a) improve adolescents' and clinicians' perception of the quality and efficiency of the visit

*Outcome Measure*s: App's Impact on Visit Quality was measured with the following items to capture the adolescents' perspectives: "The App improved the quality of my health care visit with my provider" "I liked the look/format of the Health-E You App", "I understood the information on the App.", "It was difficult to move through the App", "I experienced information overload using the App", "I would recommend this App to a friend", "I liked the video(s) of the health care provider", and "I liked the videos of teens talking about birth control". Likert scale (options 1=strongly disagree to 5=strongly agree); then dichotomized into agrees versus neutral/disagrees.

The following items captured the providers' perspectives: Provider Perceptions of App's Impact was assessed with the following items: "Helps engage teens in the contraceptive decision making process"; "Helps me provide a more individually-tailored discussion around contraceptive options"; "Helps me integrate reproductive health into all visit types (non-reproductive related health visits)", "Makes my clinic schedule run behind" and time spent on providing contraceptive care as measured by the following questions: "How much time did you spend providing basic contraceptive information", "How much time did you spend screening for potential medical contraindications for contraception" and How much time did you spend identifying what contraceptive method(s) would be the best fit for your patient?" Time to conduct activities was rated on a 5-point scale (1=did not spend any time to 5=a lot of time). Items were scored using a Likert scale (1= strongly disagree to 5=strongly agree); then dichotomized into agrees versus neutral/disagrees.

Rationale: The perceptions of both adolescents and providers are key in assessing the utility of the app on clinical practice. Provider stakeholders stated that it in order for health technologies to be adopted into clinical practice they should support them in delivering clinical care which makes the visit more efficient and effective. Similarly, adolescents wanted the technology to be of value for their visit to enhance engagement, satisfaction and utility of the app. These measures help identify the benefits of implementing the app within clinics. These questions provide important information on the acceptability, feasibility, and value of implementing the App into clinical practice from both the provider and patient perspectives.

Purpose: To assess provider and adolescents ratings of how the app improved the effectiveness of the visit; providers' ability to provide more tailored discussion of contraception options during their clinic visits; adolescents' engagement in decision making from the provider perspective; the extent to which the app improved their ability to integrate reproductive health into all visit types; and the impact on timing/patient flow.

2b) increase the proportion of visits where adolescents and clinicians discussed contraception

Outcome Measures: Percentage of Adolescent Participants Who Report Discussing Birth Control with Health Care Provider at Visit. This was a secondary outcome measure that was asked of adolescents at the 48-hour follow up. Participants responded to the single item- "At your visit, did you discuss birth control with your health care provider?" via a self-administered survey and was a dichotomous yes-no measure.

Rationale: Provider discussion on birth control at the health care visit is a central component of the Health-E You clinical intervention. The app was designed as a contraception decision support tool aimed to facilitate communication about sexual health between adolescents and their provider. Thus, this question aims to gather information about how the app influenced patient-provider communication at the visit. Activating/empowering patients to seek the care they need is an important component of patient-centered contraceptive care.

Purpose: To examine the impact the app had on improving the proportion of adolescent and providers who discussed birth control at the visit by comparing differences in the Intervention and Control arms.

Aim 3: Evaluate the effectiveness of the Health-E You contraceptive app to reduce the incidence of unprotected sexual intercourse (and associated unintended pregnancies) among Latina adolescent girls.

3a) increase the proportion of sexually active adolescents who receive an effective contraceptive at their clinic visit

Outcome Measure: The primary outcome is the proportion of adolescent participants who report receipt of a non-barrier contraceptive method at their visit, a prescription for contraception or a follow-up appointment/referral for contraception. This was assessed at the 48-hour follow-up survey for both intervention and controls. Participants responded to the query of "Which of the following happened at this visit" (recent visit with your health care provider in which you used the Health-E You App via a self-administered survey at the 48-hour follow up): 1) Received birth control; 2) Made an appointment to receive contraception in the future; 3) Received prescription of hormonal contraception; 4) Did not receive a birth control prescription, referral or actual method.

Rationale: Receipt of effective non-barrier contraceptive methods is a central component reflecting the efficacy of the App to improve effective contraceptive use in this population. This measure helps to identify what happened during the health care visit, and to see if the Health-E You App improved the youth's receipt of contraceptive services during their clinical visit.

Purpose: To assess the effectiveness of the app in improving the proportion of adolescents who receive contraception at their visit where they used the app.

3b) increase the proportion of sexually active adolescents who adhere to an effective contraceptive method over time -- at three and six months after their clinic visit.

Outcome Measure: This primary outcome measure was: self-reported use of non-barrier contraception in the prior 3 Months (along with type of contraceptive) assessed at baseline, 48 hour, 3- and 6 month follow-ups. Contraceptive methods were

dichotomized into non-barrier methods versus other methods/nothing used. In addition, change in contraceptive method efficacy was tracked over time. The list of methods included the following: 1) shot; 2) birth control pills; 3) patch; 4) ring; 4) male condoms; 5) female condoms; 6) pull-out/withdrawal; 7) rhythm/calendar; and 8) Other. Non-barrier contraception are categorized by tiers of effectiveness (CDC, WHO). The continuum of effectiveness of methods starting with least effective was coded as follows: (1) using nothing; (2) birth control pills, the patch, or the ring; (3) the shot; (4) IUD or Implant. IUD and implant were not included in the baseline list because adolescents using either were not eligible to participate; however they were listed for the 3- and 6- month follow-ups.

Rationale: This measure was used to assess the type of contraception used at each time point in order to understand the extent to which the app helped to support youth in selecting a more effective method of contraception to achieve their self-reported goal of avoiding a pregnancy.

Purpose: There were two purposes of this measure: 1) to examine differences in non-barrier contraceptive use between app users and controls over time (baseline, 3- and 6-month follow-up) and 2) it also was used to assess changes in contraceptive use over time to see if the app increased the arm (app users) use of more effective methods compared to controls.

Sample Size Calculations and Power

In designing this study, we adhered to the criteria of the PCORI methodology principals that pertain to the development of research questions.[iii] We used preliminary studies to estimate that approximately 80% of the eligible adolescents would agree to participate. The goal was to enroll a total sample of **1400** sexually active Latina girls aged 14-18 in the study (700 per treatment group). Sample size estimates and power analyses were based on a 40% attrition rate by the 3-month follow up (**840** total, 420 per treatment group) and another 10% by the 6-month follow-up (**700** total, 350 per treatment group).

Assuming power = .80 and alpha = .05, the minimum detectable difference in the primary behavioral outcome at each time point between the intervention and the control condition is 12-14, 18-19 or 22-23 percentage points depending on whether the intraclass correlation (ICC) assessing the

clustering effect of clinics is low, moderate, or high. Prevalence of outcomes in the control condition come from the final data set after completion of data collection, and the ICC range is suggested by data from Reading et al.[iv] The calculated differences in proportions translate into an effect size (Cohen's h) falling between a small (h=.20) and medium (h=.50) effect size for all three levels of ICC. Specifically, regarding evaluation of the intervention condition, the minimum achievable precision for point estimates of proportions is a confidence interval width of 11 percentage points for visit data~~,~~ and 12 percentage points for 3-month data and 6- month data.

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Table 1: Power Analysis

	Minimum detectable change if:				
Outcome	% of Baseline Sample (N)	Control Proportion	ICC=.01 Change (h)	ICC=.05 Change (h)	ICC=.09 Change (h)
Receive effective method at visit*	37% (505)	39%	+14% (.282)	+19% (.380)	+23% (.456)
Use effective method at 3 months	45% (616)	45%	+13% (.26)	+18% (.365)	+22% (.445)
Use effective method at 6 months	49% (669)	33%	+12% (.255)	+18% (.361)	+22% (.441)

* Analysis is limited to participants not already using an effective contraceptive method.

Time Frame for the Study

Participant recruitment took place from August 2016 to May 2018 and was most active during the school year when SBHCs were fully operational. Recruitment continued during the summer months, but was limited due to staffing and fewer students on campus. Follow-up procedures continued through December 2018.

To evaluate the effectiveness of the app, the research team compared differences between the intervention and control group prior to the intervention (at baseline), within 48 hours of the visit and at 3-month and 6-month follow-up periods. These follow-up time points were selected for a number of reasons. Oral contraceptives are the most commonly used non-barrier contraceptive, and they have high rates of discontinuation within the initial 3-month period.[v] In addition, unprotected sex

among adolescents, including use of the withdrawal method, is high.[vi] Furthermore, while there is little research on discontinuation rates for LARCs, a recent study (among women 25 years and younger) found that discontinuation rates are generally low and do not vary much between 6 and 12 months, thus a 6-month follow-up was deemed adequate.[vii]

Data Collection and Sources

Follow-up procedures are designed to maximize participant retention over time and minimize bias due to attrition. Youth were informed that they would receive a financial incentive of up to US$70 for completing all follow-up surveys. The following is the incentive structure:

- US$10 for completing the baseline information and immediate follow-up survey,
- US$20 for completing the 3-month follow-up assessment,
- US$20 for completing the 6-month follow-up,
- US$20 bonus for completing all surveys.

Participants were enrolled in the study for a total of six months (with one additional month to complete follow-up surveys) following their initial clinic visit, where they interacted with our Health-E You app or completed the baseline survey. We also collected the youth's preferred method of contact (e-mail and, or cell phone) to provide them with their follow-up surveys and e-gift cards. We also explained that their participation was completely confidential.

Each participant was sent their survey link by email and / or text. Non-respondents received up to three reminders to complete their follow-up survey. Those who provided phone information were also contacted by phone to either complete the survey immediately by phone or to have the link resent to them. Participants had one week to complete the immediate follow-up survey and up to 30 days to complete the 3 and 6 month follow-up surveys. In addition, we designed our follow-up surveys so that we can capture data from participants who did not respond to previous follow-up surveys. This was an additional strategy to reduce our overall attrition.

We were unable to ascertain exactly why individual participants were lost to follow-up because of the remote nature of the study. However, while conducting follow-up procedures, our team noted that many phone numbers had changed or were no longer valid, or e-mails bounced back. This population is of Latina background and we heard two issues that impacted the study. One is that participants return to visit family members in Mexico for extended time periods. Another was concerns over immigration “crackdowns” and were worried that sharing contact information may put family members and/or friends at risk – regardless of the participant’s immigration status.

Analytical and statistical approaches

We assessed the effect of the intervention by looking for differences over time between the control (usual care) group and intervention (Health-E You app) group in contraception use self-efficacy and self-reported use of non-barrier contraception at follow-up. Specifically we hypothesized, assuming group equivalence at baseline, that 3 months and 6 months post-baseline the intervention group, compared to the control group, would have higher mean contraception use self-efficacy (Aim 1c, Primary Outcome 2) and a higher proportion would be using effective (i.e., non-barrier) contraception (pill, patch, ring, shot, IUD, or implant) (Aim3b, Primary Outcome 3).

We assessed the effect of the intervention using generalized mixed effects models estimated by maximum likelihood (mixed effects linear regression to assess self-efficacy, mixed effects logistic regression to assess non-barrier contraception use). These models included the repeated outcome measure as the response variable as well as terms for the intercept, an indicator of treatment of group (intervention vs. control), a time effect (baseline, 3-month follow-up, 6-month follow-up), the time by treatment group interaction, and three covariates that clinical experience and thre research literature suggest could influence the outcome: age (rage was 14-18), whether the purpose of the clinic visit was related to pregnancy or contraception (a time invariant covariate), and whether the participant engaged in sexual intercourse in the past 3 months (a time varying covariate). We fit models with random intercepts and slopes over time to accommodate the repeated measures gathered from each subject and to allow subject-specific changes in the responses over time. The time treatment group interaction was the direct test if the intervention effect. Computation of p-values was based on robust variance estimation that adjusted for a potential lack of independence between observations due to clustering by recruitment site (SBHC).

We also hypothesized that mean contraception use self-efficacy would be higher in the intervention group than the control group immediately after the clinic visit (Aim 1b, Primary Outcome 1). The same analytic approach already described was implemented to assess this hypothesis with the exception that the mixed effects linear regression model included only two time points: baseline and 48 hours after baseline (which changed the sexual activity covariate to being time invariant).

Among intervention group participants only contraception knowledge was assessed immediately prior to using the *Health-E You* app and immediately after app use. We predicted mean knowledge would increase from the pre-app assessment to the post-app assessment (Aim 1a, Secondary

Outcome 1). Once again, a mixed effects linear regression analysis was employed with two time points, the same covariates, and robust variance estimation (to account for clustering by SBHC). However, since the control group was not part of the analysis, the model did not include parameters representing treatment group or the time by treatment group interaction. In this model, the time parameter was the direct test of the intervention effect.

Finally, we hypothesized that at the clinic visit (the visit immediately following recruitment and, in the intervention condition, use of the app) a higher proportion of the intervention group, when compared to the control group, would discuss birth control with the clinician (Aim 2b, Secondary Outcome 2) and receive a non-barrier method of birth control either directly or via an appointment or referral (Aim 3a, Secondary Outcome 3). These hypotheses were tested using logistic regression models regressing the dichotomous (yes-no) outcomes on treatment group (the direct test of the intervention effect), age, purpose of visit, and whether sexually active in the prior 3 months using robust variance estimation (to account for clustering by SBHC).

Handling Missing Data

Since each assessment involves a relatively brief self-administered instrument, the amount of missing data due to failure to provide data was minimal. The largest source of missing data was participant dropout. Of the 1360 participants in the study cohort 778 (57.2%) responded to the 48-hour survey, 681 (50.1%) responded to the 3-month survey, 676 (49.7%) responded to the 6-month survey, and 575 (42.3%) responded to both the 3-month survey and the 6-month survey. Consequently, to minimize bias due to attrition, we employed multiple imputation so that every regression model could be fit to all available data while invoking the mild assumption that the data were missing at random. Imputation was performed on the data in wide format (one record per case) to correctly account for dependence in multiple observations per case. In models testing a time by treatment group, missing data were imputed separately for intervention cases and control cases. Imputation models contained all variables in the analysis model (including the outcome), baseline variables identified as correlates of retention, and indicator variables representing recruitment site (SBHC).

Heterogeneity of Treatment Effects

A concern in any cluster randomized control trial is whether or not the treatment effect is robust across sites. However, small per site sample sizes preclude direct comparisons between sites because of a lack of statistical power. We investigated the sensitivity of the intervention effect to recruitment site (SBHC) in the two primary outcomes where we assessed changes from baseline to

3-month and 6-month follow-up: contraception use self-efficacy (Aim 1c, Primary Outcome 2) and non-barrier contraception use (Aim 3b, Primary Outcome 3). For both outcomes, the time by treatment group interaction served as the direct test of the intervention effect. With three time points and two treatment groups, the interaction was represented by two parameter estimates. The sensitivity analysis employed a jack-knife technique where the analysis is repeated but with participants from one intervention SBHC removed from the analysis. Since there were 9 SBHCs randomly assigned to each treatment group, the jack-knife technique required 9 new models be assessed.

Table 2 reports the point estimate, 95% confidence interval, and p-value for each parameter obtained from the mixed effects regression analysis model including all 9 intervention SBHCs plus the range of parameter estimates and p-values obtained from the jack-knife analyses (models that included only 8 intervention SBHCs).

Table 2. Parameter Estimates from Sensitivity Analyses Compared to Parameter Estimates from Analytic Models for Two Primary Outcomes

	Interaction	Analytic Model			Sensitivity Analyses	
Outcome	Parameter	Estimate	95% CI	p-value	Estimates	p-value
Contraception	1	0.816	-0.482, 2.115	.218	0.477-1.086	.098-.408
Use Self-efficacy	2	1.576	0.377, 2.774	.010	1.269-1.729	.006-.037
Non-barrier	1	1.190	0.043, 2.338	.042	1.128-1.350	.024-.063
Contraception	2	1.711	0.529, 2.544	.005	1.511-1.936	.003-.012

For both outcomes, the data suggest the intervention effect is not sensitive to recruitment site (SBHC).

Changes to the original study protocol

The only change made to the original study protocol was extending the participant recruitment period to May 2018. Participant recruitment was originally set to end in June 2017, but the study team and PCORI Program Officer agreed to extend in order to meet recruitment goals. This change was approved by PCORI, the research team, community partners, SBHC managers, and the UCSF IRB.

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