A MOBILE HEALTH INTERVENTION TO INCREASE UPTAKE OF PRENATAL CARE IN SYRIAN REFUGEE POPULATION IN TURKEY

Study Protocol and Statistical Analysis Plan (SAP)

Protocol Identification Number: HeraInc

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09/02/2021

STATISTICAL ANALYSIS PLAN (SAP)

A MOBILE HEALTH INTERVENTION TO INCREASE UPTAKE OF PRENATAL CARE IN SYRIAN REFUGEE POPULATION IN TURKEY

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Clinicaltrials.gov Identifier	XXXXXX
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SAP Version and date	0.1 (08/31/2021)
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1. **Signature page**

Principal Investigator

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2. Abbreviations

WHO	World Health Organization
MoH	Ministry of Health
HERA	Health Recording Application

3. Table of contents

4. Modification History

Unique Identifier for SAP Version	Date of SAP Version	Authors	Changes From the Previous Version
Draft V0.1	08/31/2021	Aral Surmeli	Not applicable – first version

5. Introduction

The purpose of this study is to assess the effectiveness of mobile phone-based appointment reminder notifications sent through the HERA app in increasing the uptake of 4 WHO recommended prenatal visits among the Syrian refugee population.

The purpose of this Statistical Analysis Plan (SAP) is to document technical and detailed specifications for the final analysis of the data collected from protocol XXXXXX.

5. 1. Background and Rationale of the Study

According to the UN, The Syrian refugee crisis is the worst humanitarian crisis since World War 2[1]. Since the start of the Syrian Civil War in 2011, 12 million Syrians have been forcibly displaced from their homes. Turkey hosts nearly 4 million of these refugees, which constitutes the largest population of refugees in the world.[2] Healthcare services are free in Turkey for the Syrian refugee population through national insurance; however, demand-side barriers such as language, not knowing where to receive care, and fear of deportation persist. Pregnant Syrian women are especially vulnerable to barriers to care. Peer-reviewed studies in Turkish hospitals indicate that refugee women are more likely to die during and after labor[3]; additionally, less than 50% of pregnant Syrians attend at least four prenatal care visits[4].

A robust body of research evidence supports the use of mobile phone-based reminder platforms to increase timely, complete access to health services. Mobile phone-based reminders have been shown in randomized controlled trials and systematic reviews to increase the uptake of various

services, including prenatal care.[5][6] A systematic review found that the majority of text message reminder interventions improved health outcomes.[7] Mobile phone penetration is high among Syrian refugees in Turkey[8] and qualitative studies demonstrate that mobile health interventions are acceptable and feasible for Syrian refugees.[9]

5. 2. Objectives

The primary objective of this study is to evaluate the impact of mobile phone-based reminders on the uptake of prenatal care among pregnant Syrian refugee women. More specifically, the study assesses the effectiveness of mobile phone-based reminders by measuring the percent increase in the number of prenatal appointments attended by intervention arm participants compared to the control arm participants.

5. 3. Hypotheses

Null hypothesis: Sending reminders on participants' upcoming appointments 2 weeks before, 1 day before, and on the day of the appointment will not have any effect on the number of appointments that are attended. Thus, the mean number of visits will not vary significantly across the 3 arms.

Alternative hypothesis: Sending reminders on participants' upcoming appointments 2 weeks before, 1 day before, and on the day of the appointment will result in a percent increase on the number of appointments that are attended by the intervention group compared to the control groups.

6. Study Methods

6. 1. Study Type

This is a behavioral intervention study using an unblinded, parallel groups, randomized controlled study design. The intervention group ("Reminder") will download and use the HERA application to receive appointment reminders through push notifications. The control group ("No reminder") will not be using the HERA application, and therefore won't be provided with any reminders. The third group will also be a non-notified control group, i.e., "No reminder" as well.

The third group's data will be collected retrospectively via hospital records. The intent of the 3rd arm is to estimate the "true" baseline for the number of visits without any extra attention given by the medical staff, in order to prevent inadvertent behavior modification through perceived observation bias.

6. 2. Study Procedure

Pregnant Syrian refugee women who are in their first trimester of pregnancy will be enrolled in the study. Participants will be enrolled from the Obstetrics and Gynecology department of refugee health clinics in Istanbul. Participants will be randomized and enrolled into intervention or either of the two control arms (refer to section 6.5. Randomization Strategy for details).
For the intervention arm, participants will be given the consent form. After having consented to participate in the study, they will be given the socioeconomic and health history form. In what follows, they will receive a 30-minutes brief about the mobile app HERA and will be asked to download it. The mobile application will automatically plan out the dates of further prenatal care appointments based on the date of the last menstruation. Participants will receive reminders in the form of push notifications for prenatal checkup dates for 6 months. Reminders will be sent at the following intervals: 1) 2 weeks before, 2) 1 day before and 3) on the day of the recommended appointment. After the recommended appointment date, participants will receive push notifications asking whether or not they went to the appointment in weekly intervals for 1 month. This reminder algorithm will be used for each prenatal checkup for a total of three appointments post the baseline visit: once in second trimester and two in third trimester, using the World Health Organization and Turkish Ministry of Health prenatal checkup calendar. At the end of 6 months of follow up time, participants in the intervention arm will be contacted via phone call to ask for any remaining appointments or unanswered notifications. Completeness of 3 prenatal care appointments post the baseline visit, as recommended by WHO and implemented by Turkish MoH will be compared to the control groups.

Participants in the informed control arm will be given the consent form and will be asked for their contact information if consented. They will also be given the socioeconomic and health history form. Participants in the non-informed control group just will be given the socioeconomic and health history form. Both the informed and non-informed control group members will be

reached out at the end of the 6-month study period to be asked about the number of prenatal care appointments they attended. If unable to be reached, retrospective chart review of the participant's medical record will be attempted, in order to obtain the number of attended prenatal care appointments.

6. 2. 1. Recruitment Strategy

Participants will be enrolled from the obstetrics and gynecology department of refugee health clinics in Istanbul, Turkey with the help of a translator (Turkish to Arabic). The enrollment will take place with the help of the physician.

6. 3. Study Population

The population included in this study are pregnant Syrian refugee women between the ages of 18 to 49, who are in their first trimester of pregnancy.

6. 3. 1. Eligibility

Inclusion Criteria:

- Having the status of "Syrian under temporary protection"
- Being in the first trimester of the pregnancy
- Initial prenatal visit
- Age equal or greater than 18 years and less than or equal to 49

Exclusion Criteria:

- Having a citizenship or a status other than "Syrian under temporary protection"
- Not owning a mobile phone
- Being unable to read and write
- Not initial prenatal visit
- Having a chronic disorder or high-risk pregnancy that requires the individual to go to the hospital frequently. Frequently is defined as more than 3 visits post the baseline visit.
- While gestating, those that develop a high-risk pregnancy that requires more than 3 visits post the baseline visit.

6. 4. Sample Size Determination

The primary outcome measure for the power and size calculation is the difference in the mean number of visits among the different arms of the study. We set our target detectable difference in means to be 0.5 or more additional visits. As the maximum standard deviation is 1.5 due to the restricted range of 0 to 3 visits, our target effect size is 0.5/1.5 = 0.33. Our calculation shows that each arm will need at least 40 patients to have a power of 90% and a two tailed significance level of 0.05. Due to the nature of refugees, we anticipate a high loss due to follow up and other reasons for dropout. Without prior information, we assume a 20% loss rate and therefore inflate the number of patients per arm by 25%. Thus, we plan to enroll 54 patients per arm for a total of 162 individuals. The statistical software G*Power Version 3.1.9.6 available from the UCLA Institute for Digital Research & Education Statistical Consulting website; G*Power (ucla.edu), was used for the calculations.

6. 5. Randomization Strategy

Subjects will be selected on the following basis: randomly select a week and recruit on 6 days of that week. On 3 of the days the selection process will start in the morning, denoted as AM, (the first part of the day that is expected to see half of the patients) and on the other 3 days the selection process will start in the afternoon, denoted as PM, (the second part of the day that is expected to see half of the patients.) For each AM/PM session, the first 27 subjects giving approval to be in the study will be randomly assigned into one of the 3 arms. It is estimated that 100 to 200 women use the hospital daily. Thus, we feel that most likely the daily target intakes will be met. However, if not met by the end of the AM/PM shift, the selection process will stop. After day 6 and before any data analysis, a check will be done on the sample sizes and additional subjects may be recruited by selecting another week to perform additional recruiting.

This sampling plan requires that the number of women coming to see the medical staff be approximately the same day to day and AM to PM.

Details of the random assignment to AM/PM and to groups are attached. The assignment of treatment and control groups to 0, 1 or 2 will be done prior to the start of subject recruitment but will not be shared with the data analyst until after the analysis is complete.

7. Outcomes

Primary Outcome:

The primary outcome of this study is the number of medical visits, following the initial baseline PNC visit, over the 6-month period prior to childbirth.

Secondary analyses:

In the secondary analyses, we will further examine other risk factors, including sociodemographic and reproductive medical history, on the number of medical visits during the study period. The following additional data will be gathered:

1. Age
2. Highest level of education
3. Current employment status and profession if employed
4. Marital status
5. If married, whether the spouse is alive or deceased
6. If married, whether the spouse resides with the participant or not
7. Number of children
8. Ages of children
9. Miscarriage history, and the number and the timing of miscarriage, if any
10. Number of deceased children, if any
11. Number of times the participant gave birth to stillborn baby, if any
12. If prior pregnancies, the number of deliveries occurred at home and at a hospital
13. Type of delivery (vaginal, C-section) and the number of each type
14. Information on prenatal care appointments made during prior pregnancies, and the number of appointments attended
15. Information on medical conditions that require long-term medication use, if yes, the name of the condition and medication
16. Duration of time living in Turkey

7.1. Populations and subgroups to be analyzed Per Protocol (PP)

All randomized study subjects not rejected over the observation period and having complete data will be the basis of the analysis. Subjects with missing data will be excluded from the analysis. This will be the primary population for the analysis.

8. Analysis

All outcomes will be presented using descriptive statistics, continuous data by the mean, standard deviation and a plot of the pdf. Binary and categorical variables will be presented in tables using counts. R version 4.0.5 will be used for all statistical analysis.

8.1. Primary Analysis

The primary analysis will be a standard one-way fixed effect ANOVA comparing the 3 arms. The resulting ANOVA results and the arm means with 95% confidence intervals will be presented.

8.2. Secondary Analysis

The effects of the sociodemographic and medical history factors on the primary outcome will be analyzed using the Poisson regression model. A standard regression results table will be presented to indicate which, if any, of these factors are significant influencers.

8.3. Missing Data

To reduce the loss-to-follow-up risks: participant phone calls and review of hospital records for subjects with missing data will be performed. Currently there are no plans for attempting a multiple imputation analysis.

8.4. Timing of Final Analysis

Final analysis will be run 6 months after the start of the randomized controlled trial, after having contacted participants.

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[2] Situation Syria Regional Refugee Response. UNHCR operational data website. https://data2.unhcr.org/en/situations/syria. Updated April 17, 2020. Accessed May 3, 2020.

[3]Ozel S, Yaman S, Kansu-Celik H, Hancerliogullari N, Balci N, Engin-Ustun Y. Obstetric Outcomes among Syrian Refugees: A Comparative Study at a Tertiary Care Maternity Hospital in Turkey. *Rev Bras Ginecol Obstet*. 2018;40(11):673-679. doi:10.1055/s-0038-1673427

[4]Roberton T, Weiss W; Jordan Health Access Study Team; Lebanon Health Access Study Team, Doocy S. Challenges in Estimating Vaccine Coverage in Refugee and Displaced Populations: Results From Household Surveys in Jordan and Lebanon. Vaccines (Basel). 2017;5(3):22. Published 2017 Aug 12. doi:10.3390/vaccines5030022

[5] Cormick G, Kim NA, Rodgers A, et al. Interest of pregnant women in the use of SMS (short message service) text messages for the improvement of perinatal and postnatal care. *Reprod Health*. 2012;9:9. Published 2012 Aug 6. doi:10.1186/1742-4755-9-9

[6] Hasvold PE, Wootton R. Use of telephone and SMS reminders to improve attendance at hospital appointments: a systematic review. *J Telemed Telecare*. 2011;17(7):358-364. doi:10.1258/jtt.2011.110707

[7] Hall AK, Cole-Lewis H, Bernhardt JM. Mobile text messaging for health: a systematic review of reviews. *Annu Rev Public Health*. 2015;36:393-415. doi:10.1146/annurev-publhealth-031914-122855

[8] Confidential Data.

[9] Mesmar S, Talhouk R, Akik C, et al. The impact of digital technology on health of populations affected by humanitarian crises: Recent innovations and current gaps. *J Public Health Policy*. 2016;37(Suppl 2):167-200. doi:10.1057/s41271-016-0040-1

STUDY PROTOCOL

A MOBILE HEALTH INTERVENTION TO INCREASE UPTAKE OF PRENATAL CARE IN SYRIAN REFUGEE POPULATION IN TURKEY

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Protocol Identification Number	HeraInc
Clinicaltrials.gov Identifier	XXXXXX
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Study Identification

Unique Protocol ID: HeraInc

Brief Title: A Mobile Health Intervention to Increase Uptake of Prenatal Care in Syrian Refugee Population in Turkey

Official Title: A Mobile Health Intervention to Increase Uptake of Prenatal Care in Syrian Refugee Population in Turkey

Study Status

Study Start: October 1, 2021
Primary Completion: October 1, 2022
Study Completion: October 1, 2022

Sponsor/Collaborators

Sponsor: HERA Inc
Responsible Party: Sponsor
Collaborators: Medical Rescue Association (MEDAK), Turkey

Oversight

Human Subjects Review Board Status: Approved
Approval Number: 2021-04/04
Board Name: Acibadem Mehmet Ali Aydınlar University Medical Research
Institutional Review Board Email: atadek@acibadem.edu.tr Address:

Study Description

Brief Summary: The purpose of this study is to assess the effectiveness of mobile phone-based appointment reminder notifications sent through the HERA app in increasing the uptake of 4 WHO recommended prenatal visits among Syrian refugee population.

Detailed Description:

Background: 12 million Syrians have been forcibly displaced from their homes since the start of Syrian Civil War in 2011. Despite Turkey providing free healthcare services through national insurance to nearly 4 million refugees that it hosts, pregnant Syrian women are less likely to attend prenatal visits and more likely to die during and after labor. An

increase in the uptake of prenatal care may improve quality of life through healthy pregnancies and safer labor conditions in this population with double vulnerability.

Mobile phone-based reminders have been shown in randomized controlled trials and systematic reviews to increase the uptake of various services, including prenatal care. Mobile phone penetration is high among Syrian refugees in Turkey and qualitative studies demonstrate that mobile health interventions are acceptable and feasible for Syrian refugees.

Primary objective: To evaluate the impact of mobile phone-based reminders on the uptake of prenatal care among pregnant Syrian refugee women. More specifically, the study assesses the effectiveness of mobile phone-based reminders by measuring the percent increase in the number of prenatal appointments attended by intervention arm participants compared to the control arm participants.

Study design: This is a behavioral intervention study using an un-blinded, parallel group, randomized controlled study design.

Recruitment strategy: Participants will be enrolled from the obstetrics and gynecology department of refugee health clinics in Istanbul, Turkey with the help of a translator (Turkish to Arabic). The enrollment will take place with the help of the physician.

Primary Outcome: The primary outcome of this study is the number of medical visits, following the initial baseline PNC visit, over the 6-month period prior to childbirth.

Secondary outcomes: Secondary outcomes are based on the Sociodemographic and Health History form. The form gathers information about demographics of the participants (age, education, employment, marital status, number of children) and health history (previous pregnancies, delivery methods, miscarriages, stillborn, chronic conditions and medications. We will further examine these risk factors on the number of medical visits during the study period.

Conditions

Conditions: Prenatal Care, Pregnancy

Keywords: Mobile health, Refugee

Study Design

Study Type: Interventional

Primary Purpose: Health Services Research

Interventional Study Model: Parallel Assignment
The intervention group cluster will use the HERA application to receive appointment reminders. The Informed and Non-Informed Control groups will not be using the HERA application.

Number of Arms: 3

Masking: None (Open Label)

Allocation: Randomized

Enrollment: 162 [Anticipated]

Arms and Interventions

Experimental: Reminder
Participants will fill the sociodemographic and health history form. Participants will receive reminders in the form of push notifications for prenatal checkup dates automatically generated according to their pregnancy start data or initial check-up appointment for 6 months. Reminders will be sent at the following intervals: 1) 2 weeks before the appointment, 2) 1 day before the appointment, and 3) on the day of appointment. After this date, participants will receive push notifications asking whether they went to the appointment or not weekly for 1 month. This reminder algorithm will be used for each prenatal checkup for a total of four appointments: once in first trimester, once in second trimester and two in third trimester, using the World Health Organization and Turkish Ministry of Health prenatal checkup calendar. At the end of 6 months of follow up period, participants will be contacted via phone call to ask for any remaining appointments or unanswered notifications.

No Intervention: Informed Control No Reminder
Participants will fill the sociodemographic and health history form. Their contact information will be gathered. Participants will be contacted at the end of 6 months and will be asked about the number of the prenatal care appointments they have attended during their pregnancy.

No Intervention: Uninformed Control No Reminder

Participants will fill the sociodemographic and health history form. No contact information will be gathered. The purpose of this arm is to estimate the "true" baseline for the number of visits without any extra attention given by the medical staff.

Outcome Measures

Primary Outcome Measure: Rate of attendance for prenatal care visits:
The number of 4 mandatory prenatal care appointments that are attended are presented here.

Secondary Outcome Measure: Sociodemographic and Health information form data: Data about sociodemographic and health information of participants will be presented here.

Eligibility

Minimum Age: 18 Years
Maximum Age: 49 Years
Sex: Female
Gender Based: No
Accepts Healthy Volunteers: Yes

Criteria:

Inclusion Criteria:

- Having the status of "Syrian under temporary protection"
- Being in the first trimester of the pregnancy
- Initial prenatal visit
- Age equal or greater than 18 years and less than or equal to 49

Exclusion Criteria:

- Having a citizenship or a status other than "Syrian under temporary protection"
- Not owning a mobile phone
- Being unable to read and write
- Not initial prenatal visit
- Having a chronic disorder or high-risk pregnancy that requires the individual to go to the hospital frequently. Frequently is defined as more than 3 visits post the baseline visit.
- While gestating, those that develop a high-risk pregnancy that requires more than 3 visits post the baseline visit.

Contacts/Locations

Central Contact Person: Aral Surmeli, MD
Telephone: +905353140179
Email: a.surmeli@medak.org.tr

Study Officials: Aral Surmeli, MD
Study Principal Investigator Founder/CEO

Sociodemographic and Health History Form (will be filled with the assistance of a translator)

1. Age:
2. What is your highest level of education?
    a. Undergraduate
    b. High School
    c. Middle School
    d. Elementary school
    e. Can read
    f. Can not read
3. Do you currently work? If yes, what is your profession?
    ……..

4. Are you married?
    a. Yes
    b. No

5. Is your spouse alive?
    a. Yes
    b. No

6. Does your spouse live with you?
    a. Yes
    b. No

7. How many children do you have?
    a. ……
    b. Doesn't have any

8. How old are your children?
    Child 1 age: ……
    Child 2 age: ……
    Child 3 age: ……
    Child 4 age: ……
    Child 5 age: ……
        If more add here:……..

9. Have you ever had a miscarriage?
    a. No
    b. Yes, …….. time(s)
    c. If yes, do you remember during which week of your pregnancy?
        ……..

10. Have you lost any children?
    a. Yes, …….. time(s)
    b. No

11. Did you ever give birth to a stillborn baby (at or after 28 weeks of gestation)?
    a. Yes, …… time(s)
    b. No

12. During your previous pregnancies, where did you give birth? (make sure to include all children)
    a. At home, …… time(s)
    b. At a hospital, …… time(s)

13. What type of delivery did you undergo? (make sure to include all children)
    a. Vaginal birth, …… time(s)
    b. C-sections, …… time(s)
        i. If C-section, what was the reason (preference, medical emergency, etc.)?
           ……..

14. Have you been to prenatal care appointments during your previous pregnancy? If yes, how many appointments have you been to?
    ……..

15. Have you been diagnosed with a medical condition (diabetes, hypertension, asthma, etc.) that requires long-term medication use?
    a. No
    b. Yes, please specify ……
        i. If yes, what's the name of the medication?
           ……

16. For how long have you been living in Turkey?
    ……