Improving pediatric COVID-19 vaccine uptake using an mHealth tool: a randomized, controlled trial

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
CDC	Centers for Disease Control
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
ECHO	Environmental Influences on Child Health Outcomes
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
ISPCTN	IDeA States Pediatric Clinical Trials Network
MedDRA	Medical Dictionary for Regulatory Activities
mHealth	Mobile Health
mITT	Modified Intent-to-Treat
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
UAMS	University of Arkansas for Medical Sciences

1. PURPOSE OF THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan (SAP) is a document intended to provide a detailed and comprehensive layout of the planned analytical methodology to be used for the multi-center randomized study of a vaccine communication mHealth app on parental decisions to vaccinate their children against coronavirus disease 2019 (COVID-19) of UAMS Protocol 273761, Improving Pediatric COVID-19 Vaccine Uptake Using an mHealth Tool: A Randomized, Controlled Trial. This SAP applies to the protocol Version 09 dated on December 16, 2022. The purpose of this plan is to provide general, and in some instances, specific guidelines from which the analysis will proceed.

2. OBJECTIVE OF THE STUDY

2.1 PRIMARY OBJECTIVE

- Determine the effect of a parent-facing, vaccination decision-making mobile health (mHealth) tool on children's COVID-19 vaccine series completion

2.2 SECONDARY OBJECTIVES

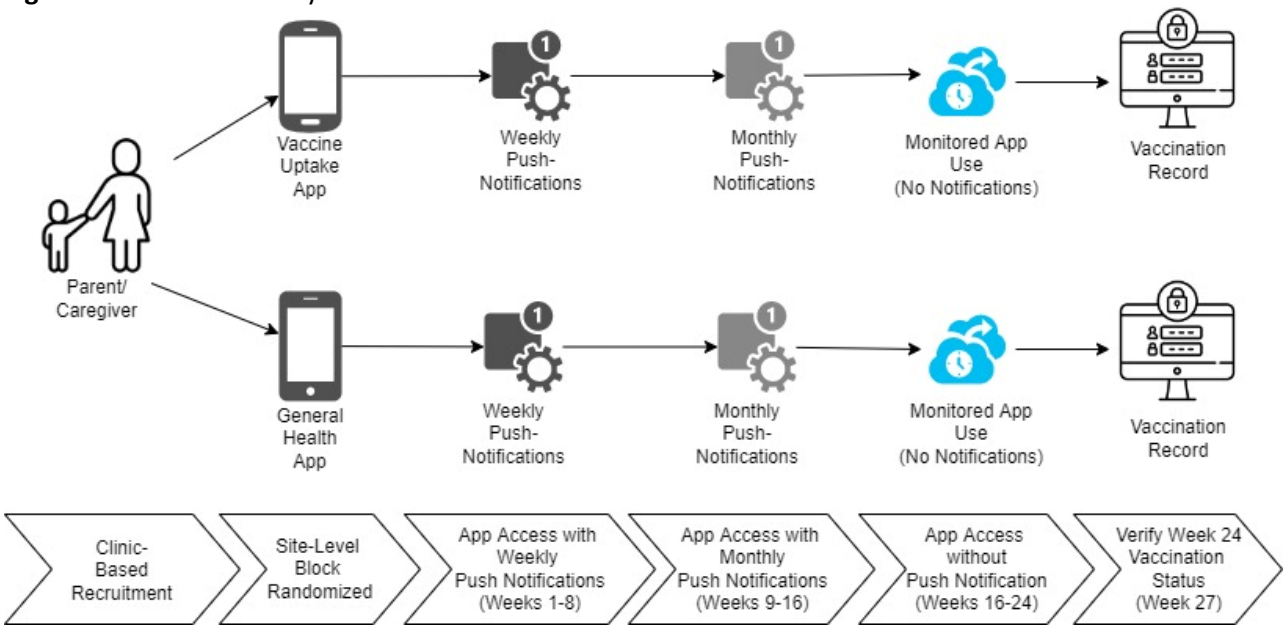
- Determine the effect of a parent-facing, vaccination decision-making mHealth tool on children's COVID-19 vaccine series initiation
- Determine the effect of a parent-facing, vaccination decision-making mHealth tool on parental attitude toward pediatric COVID-19 vaccination

3. STUDY OVERVIEW

3.1 STUDY DESIGN

This multi-site, parallel, randomized, controlled trial will assign parents/caregivers of children eligible to receive COVID-19 vaccine seen at participating clinics to receive either the mHealth Vaccine Uptake app or the General Health app containing general infection and child health topics. Randomization will be stratified by clinic using a permuted block design with varying block size. Outcome is receipt of COVID-19 vaccine by the parents'/caregivers' children.

Figure 1: Schema of study intervention



3.2 RANDOMIZATION AND BLINDING

3.2.1 Randomization

The study will use a 1:1 parallel design at the caregiver level to assign caregivers to the intervention (Vaccine Uptake app) or the control (General Health app) arm. The study team will stratify randomization by participating clinic and in varying block of participants using a permuted design. Randomization will occur after enrollment and before the baseline assessment.

3.2.2 Masking

Masking is not planned for this study.

3.3 SAMPLE SIZE

The primary outcome for this study is the proportion of unvaccinated children who complete the COVID-19 vaccine series during the study period. The underlying assumption, based on available data for ISPCTN site states, is that without the mHealth intervention, the COVID-19 vaccine uptake would occur in 30% of children. [1]

Justification of primary outcome effect size. Table 1 summarizes vaccination rates among children 12-17 years old through July 31, 2021, as published by the CDC.[2] Based on these data, we see that vaccination rates decline with decreasing age and that ECHO ISPCTN states demonstrate a trend toward lower overall and by-age vaccination rates. When excluding Vermont, Rhode Island, and New Hampshire (states that are part of the highest regional vaccine uptake rates in the US), the other 15 ECHO ISPCTN states have vaccination rates significantly lower than non-IDeA states. Assuming that cumulative vaccination rates continue to increase over time and that vaccination rates for children <12 years old will continue the trend toward lower vaccination rates, we anticipate that 30% overall vaccination rates among eligible children at the time of study launch is reasonable.

Table 1. Proportion of Children 12-17 yrs. old who completed COVID-19 vaccination by July 31, 2021

	12-17 Med[IQR]	16-17 years old	14-15 years old	12-13 years old
Overall	30% [25%-42%]	40% [32%-51%]	29% [24%-41%]	24% [19%-34%]
IDeA State Residents	24% [20%-37%]	33% [26%-49%]	23% [19%-35%]	20% [14%-32%]
IDeA State Residents (excluding New England)	23% [19%-36%]*	31% {26%-45%]	22% [18%-29%]	19% [14%-31%]
Non-IDeA State Residents	32% [25%-42%]	41% [32%-51%]	29% [24%-41%]	25% [19%-34%]
***Difference from non-IDeA state residents (p=0.028)**				

We based the 10% increase in vaccination rates on the cumulative estimated effects of intervention components within the Vaccine Uptake app. As discussed in the Background, behavioral nudges such as text messages (i.e., push notifications within the app) are associated with a 5% increase in vaccination rates.[3] App-based education and communication has shown variable increases in vaccination rates and intent to vaccinate, up to 8-10%.[4,5] Thus, a combined 10% increase in vaccination rates is reasonable to expect from the Vaccine Uptake app since it combines multiple approaches in the same intervention.

Public Health Impact. In this study, we are estimating that using the Vaccine Uptake app will result in a 10% increase in the proportion of children who will complete COVID-19 vaccination. When looking at the impact of a 10% increase in pediatric vaccination rates, based on a US population of 53.7 million children 5-17 years of age,[6] such an increase would result in an additional 5 million vaccinated children. Previous research has shown that app-based vaccine uptake interventions are less costly than more traditional methods, such as paper handouts and communication tools. We estimate a cost of $10,000 dollars for the first year of a customized version of the

Vaccine Uptake app per state. Deployment of the Vaccine Uptake app nationally would cost a little as $500,000 dollars per year, or 10 cents per additional child who completes COVID-19 vaccination.

In determining sample size, each caregiver is considered to be a cluster with an average of 2 unvaccinated children. To demonstrate an improvement in the proportion of unvaccinated children of caregivers who complete the COVID-19 vaccination series due to the mHealth intervention from 30% to 40%[7,8,9] would require 758 caregivers (379 per arm), at the two-sided 0.05 significance level with power of 0.90 and an intraclass correlation coefficient of 0.60. The table below shows the sample size needed to have 90% power to detect a 10-percentage point increase in the proportion of children who complete the vaccination series using the Vaccine Uptake app with varying levels of intraclass correlation. To ensure that there are at least 758 caregivers, the primary analysis population, we expect to randomize 892 caregivers to account for up to 15% of randomized participants who do not use the Vaccine Uptake app or General Health app after downloading it during enrollment.

Intraclass Correlation Coefficient	Sample Size
0.40	331 per arm (662 total)
0.50	355 per arm (710 total)
0.60	379 per arm (758 total)
0.70	402 per arm (804 total)
0.80	426 per arm (852 total)

4. STUDY ENDPOINTS AND DEFINITIONS

4.1 PRIMARY ENDPOINT

1. Proportion of children who complete COVID-19 vaccination, as verified in state, clinic, or participant-held records

Def: Completion of COVID-19 vaccination will be coded as 1=Yes or 0=No. Verification of vaccine receipt will occur by any of the following methods:

- Photograph of the child's vaccine card, furnished by the caregiver
- Medical records documentation of child vaccine receipt
- Recorded vaccine receipt in the appropriate state vaccine registry

4.1 SECONDARY ENDPOINTS

1. Proportion of children who receive ≥ 1 dose of the COVID-19 vaccination series, as verified in state, clinic, or participant-held records

Def: Initiation of the COVID-19 vaccination series will be coded as 1=Yes or 0 = No. Verification of vaccine receipt will occur by any of the following methods:

- Photograph of the child's vaccine card, furnished by the caregiver
- Medical records documentation of child vaccine receipt
- Recorded vaccine receipt in the appropriate state vaccine registry

2. Change in enrolled parent/caregiver domain scores from baseline to week 16 on the modified SAGE Vaccine Hesitancy Scale adapted for the COVID-19 Vaccine

Def: The modified SAGE Vaccine Hesitancy Scale includes ten statements with ordinal responses using a 5-point Liker scale (1 = Strongly Disagree; 2 = Somewhat Disagree; 3 = Neutral; 4 = Somewhat Agree; 5 = Strongly Agree). A composite vaccine hesitancy score will be the sum of the 10 items/statements after reverse coding items 1, 2, 3, 4, 6, 7, and 8 (range of 10 to 50). The reverse coding makes directionality uniform across the ten items so that a higher composite score indicates more hesitancy.[10] Additionally, each statement/item will be treated as an individual outcome measure of hesitancy (range of 1 to 5).

5. STATISTICAL PRINCIPALS

5.1 GENERAL APPROACH

The statistical team will conduct all statistical analyses following the statistical principles for clinical trials as specified in ICH Statistical Principles for Clinical Trials (ICH Topic E9). The study team will describe and justify any deviations from the planned analyses in the final integrated clinical study report. The study team will present all study data and summary tables for the overall study and by study sites.

The statistical team will summarize descriptive statistics for continuous data by using mean and standard deviation or median and interquartile range, as appropriate. The team will also summarize categorical data by using frequency and percent.

The statistical software package SAS Version 9.4 or higher (SAS Institute, Cary, NC, USA) or STATA version 14 or higher (Stata Statistical Software, College Station, TX: StatCorp LLC) will be used to perform all analyses and to summarize data.

5.2 STATISTICAL SIGNIFICANCE AND CONFIDENCE INTERVALS

Unless otherwise specified, statistical tests will be 2-sided for all analyses and the null hypothesis will be rejected at the significance level of $\alpha = 0.05$. P-values will be rounded to four decimal places before assessing statistical significance. All confidence intervals presented will be 95% and two-sided.

5.3 POPULATIONS FOR ANALYSES

This study will have three analysis populations:

1. ITT population – This population will include all participants randomized into the study.
2. Modified ITT (mITT) population – This population will include all participants who are randomized into the study, were eligible for the study, and completed at least one session in the app involving the use of at least one pathway.
3. Per-protocol (PP) population - This population will include all participants in the mITT population who were maintained in the study for the full 27 weeks.

The primary population for analysis will be the ITT population. Study statisticians will perform additional analyses on the PP and mITT populations.

6.0 STATISTICAL ANALYSES

6.1 BASELINE DESCRIPTIVE STATISTICS

The statistical team will summarize baseline and demographic characteristics by intervention group and will apply summary statistics for both continuous and categorical variables. For continuous variables, descriptive measures will include number of non-missing values, mean, standard deviation, median, minimum, and

maximum. For categorical variables, descriptive statistics will include frequency counts and percentages by category.

Table 2: Overall descriptive summary of parent/caregiver and children characteristics

Parent/caregiver Variables	**Vaccine Uptake App**	**General Health App**	**Total**
Female, N (%)			
Ethnicity, N (%)			
Race, N (%)			
Rurality (self-reported), N (%)			
Insurance			
Etc….			
Children Variables			
Female, N (%)			
Ethnicity, N (%)			
Race, N (%)			
Age group, N (%)			
Etc….			

Table 3: Descriptive summary of parent/caregiver and children characteristics (by site)

Site		**Vaccine Uptake App**	**General Health App**	**Total**
1	**Parent/caregiver Variables**			
	Female, N (%)			
	Ethnicity, N (%)			
	Race, N (%)			
	Rurality (self-reported), N (%)			
	Insurance			
	Etc….			
1	**Children Variables**			
	Female, N (%)			
	Ethnicity, N (%)			
	Race, N (%)			
	Age group, N (%)			
	Etc….			
Etc…				

6.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

For the primary efficacy measure, we will test the following null hypothesis:

H_0: Vaccination series completion rate among children of caregivers assigned to the Vaccine Uptake app will not differ from the vaccine series completion rate among children of caregivers assigned to the General Health app

vs

H_1: Unvaccinated children of caregivers assigned to the Vaccine Uptake app will be more likely to achieve COVID-19 vaccine series completion than those children whose caregivers are assigned to the General Health app

For each vaccine-eligible child, the primary endpoint will be whether or not the child initiates and completes the COVID-19 vaccine series during the 24 weeks of the intervention period. The study team will define vaccine series completion as per the current ACIP guidance for the vaccine product. For children who receive a product that requires more than 2 doses for the primary series, receipt of up to 3 doses will be considered complete. Vaccine doses will only be valid for study purposes if given within the 24 weeks of study participation. Additional doses, when required for primary series completion, will only be valid if they are in accordance with ACIP-recommended interval minus a 4-day grace period, in accordance with recommendations of the ACIP. Also, per ACIP, there will be no maximum interval between valid doses. Incorrect second vaccine product (i.e., mixed series) will be invalid for study purposes.

Univariate Analysis

The primary endpoint will be collected as a dichotomous variable (yes/no). We will report the probability of COVID-19 vaccine series completion for each intervention group (Vaccine Uptake app vs General Health app). Initially, an unadjusted non-modeling approach using SAS PROC FREQ will be used estimate the relative risk (RR) for COVID-19 vaccine series completion (with Wald 95% CI), with the General Health app intervention group as the reference group. The analysis will be performed for all three populations (ITT, mITT, and PP).

Primary and Multivariable Analysis

A mixed-effect Poisson regression with robust error variance will be used to report adjusted relative risk (RR) with 95% CI accounting for site random effect and controlling for clustering by caregiver. The multivariable model will allow adjustment for covariates. The analysis will be performed for all three populations (ITT, mITT, and PP).

6.3 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINT(S)

6.3.1 Vaccine Series Initiation

For the secondary efficacy measure, we will test the following null hypothesis:

H_0: Vaccination series initiation rate among children of caregivers assigned to the Vaccine Uptake app will not differ from the vaccine series initiation rate among children of caregivers assigned to the General Health app

vs

H_1: Unvaccinated children of caregivers assigned to the Vaccine Uptake app will be more likely to achieve COVID-19 vaccine series initiation than those children whose caregivers are assigned to the General Health app

For each vaccine-eligible child, this secondary endpoint will be defined as whether or not the child initiates the COVID-19 vaccine series during the 16 weeks of study participation. Vaccine series initiation will be receipt of at least 1 valid dose of any COVID-19 vaccine product. Vaccine doses for series initiation will only be valid for study purposes if given within the 16 weeks of study participation.

Univariate Analysis

The secondary vaccine series initiation endpoint will be collected as a dichotomous variable (yes/no). We will report the probability of COVID-19 vaccine series initiation for each intervention group (Vaccine Uptake app vs General Health app). Initially, an unadjusted non-modeling approach using SAS PROC FREQ will be used estimate the relative risk (RR) for COVID-19 vaccine series initiation (with Wald 95% CI), with the General Health app intervention group as the reference group. The analysis will be performed for all three populations (ITT, mITT, and PP).

Secondary and Multivariable Analysis

A mixed-effect Poisson regression with robust error variance will be used to report adjusted relative risk (RR) with 95% CI accounting for site random effect and controlling for clustering by caregiver. The multivariable model will allow adjustment for covariates. The analysis will be performed for all three populations (ITT, mITT, and PP).

6.3.2 Parental Attitude Toward Pediatric COVID-19 Vaccination

The study team will evaluate parental attitude toward pediatric COVID-19 vaccination by using the modified SAGE Vaccine Hesitancy Scale that includes ten statements with ordinal responses using a 5-point Likert scale. At baseline and week 16, the study statisticians will generate summary statistics and graphical display for each of the 10 questions for the two intervention groups.

Analysis for SAGE Vaccine Hesitancy Scale Items

For each item, the study statisticians will report response frequency overall and by intervention groups. A mean score chi-square test (i.e., test of location shift) will be used to examine the association between responses and intervention groups. For the adjusted analysis, a linear mixed model will be used to account for parent/caregivers nested within clinics and allow adjustment for covariates. The analysis will be performed for all three populations (ITT, mITT, and PP).

Analysis for SAGE Vaccine Hesitancy Scale Composite

A composite vaccine hesitancy score will be the sum of the 10 items/statements after reverse coding items 1, 2, 3, 4, 6, 7, and 8 (range of 10 to 50). The study statisticians will provide summary statistics including means and standard deviation at baseline and week 16. A linear mixed model will be used to account for parent/caregivers nested within clinics and allow adjustment for covariates. The analysis team will report point estimates for the intervention group mean difference along with 95% CI. The analysis will be performed for all three populations (ITT, mITT, and PP).

6.4 ANALYSIS OF SAFETY ENDPOINTS

Because this study is of an educational intervention and poses minimal risk, adverse events (AEs) and serious adverse events (SAEs) are not expected. The study team will not solicit AEs or SAEs but will provide all participants with a site-specific telephone number to report AEs/SAEs. The study team will track severe and serious AEs that are potentially study related.

All AEs recorded during the study period will be coded with Medical Dictionary for Regulatory Activities (MedDRA) Version March 2018. Summaries of AE will be tabulated for the following types:

- Numbers (%) of participants with any AE
- Numbers (%) of participants with any SAE
- Numbers (%) of participants withdrawn from intervention due to AE

All reported AEs will be assigned the system organ class and preferred term according to MedDRA. Listing of all AEs will be tabulated by intervention group and by system organ class and preferred term.

6.5 SUB-GROUP ANALYSES

If there are enough study participants in specific racial/ethnic categories and or urban/rural and/or age group categories, the study team will perform the planned analyses for the primary efficacy analyses within subgroups.

6.6 SENSITIVITY ANALYSIS

While some participants may choose not to use the app beyond the initial download session, their outcomes will still be assessed and used to determine efficacy of the intervention. App interactions—or lack thereof—will be informative to understanding how participants engage with delivered content and how those interactions—or lack thereof—correlate with primary and secondary endpoints. The statistical team will use logistic regression analyses to determine the association between mHealth usage levels and completion or initiation of COVID-19 vaccine series.

7.0 REFERENCES

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Appendix A

Modified SAGE Vaccine Hesitancy Scale

Childhood vaccines are important for my child's health. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

Childhood vaccines are effective. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

Having my child vaccinated is important for the health of others in my community. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

All childhood vaccines offered by the government program in my community are beneficial. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

New vaccines carry more risks than older vaccines. *

- ◯ Strongly Disagree

- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

The information I receive about vaccines from the vaccine program is reliable and trustworthy. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

Getting vaccines is a good way to protect my child/children from disease. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

Generally, I do what my doctor or health care provider recommends about vaccines for my child/children. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree

I am concerned about serious adverse effects of vaccines. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree

- ◯ Strongly Agree

My child/children does or do not need vaccines for diseases that are not common anymore. *

- ◯ Strongly Disagree
- ◯ Somewhat Disagree
- ◯ Neutral
- ◯ Somewhat Agree
- ◯ Strongly Agree