Study Protocol: Increasing Influenza Vaccination in Individuals with Cardiovascular Conditions: Assessing the Effectiveness of a Digital Intervention in a Decentralized Randomized Controlled Trial

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List of Abbreviations

IRB	Institutional Review Board
LAR	Legally Authorized Representative
PII	Personally Identifiable Information
TLS	Transport Layer Security
CDC	Centers for Disease Control and Prevention
ePRO	Electronic Patient Reported Outcomes
RCT	Randomized Controlled Trial
CVD-I	Cardiovascular disease-intervention
CVD-C	Cardiovascular disease-control

Statement of Compliance

The protocol, Data Usage Agreement & Permissions form, recruitment materials, and all participant materials will be submitted to the Solutions Institutional Review Board for review and approval. Approval of both the protocol and the Data Usage Agreement & Permissions form must be obtained before any participant is enrolled. Any amendment to the protocol or Data Usage Agreement & Permissions form will require review and approval by Solutions IRB before the changes are implemented to the study. A determination will be made regarding whether a new Data Usage Agreement & Permissions form needs to be obtained from participants who provided agreement to participate using a previously approved Data Usage Agreement & Permissions form.

Protocol Summary

Title	Increasing Influenza Vaccination in Individuals with Cardiovascular Conditions: Assessing the Effectiveness of a Digital Intervention in a Decentralized Randomized Controlled Trial
Study Design	A 6-month prospective, digital randomized controlled trial targeting approximately 35,000 individuals to evaluate the effectiveness of an influenza vaccination intervention during influenza season for people with cardiovascular conditions
Objectives	*Primary:* To determine the effectiveness of a digital intervention designed to increase influenza vaccination rates in individuals with cardiovascular disease (CVD) by examining: ● Differences in self-reported influenza vaccination rates between individuals with cardiovascular disease who receive a targeted digital intervention (CVD-I) aimed at increasing influenza vaccination and those with cardiovascular disease who received no intervention (CVD-C) by the end of the study period *Secondary:* 1) To examine differences in vaccination rates between individuals in the intervention group who engaged with different numbers of intervention messages, and changes in self-reported vaccination rates following intervention messages

	2) To describe levels of engagement with the intervention messages and perceptions of the intervention messages within the CVD-I group 3) To examine predictors of vaccination status, including cardiovascular condition type, vaccine drivers/barriers, and vaccine knowledge, across diagnoses and within CVD-I and CVD-C groups *Exploratory:* 1) To examine the potential impact of COVID-19 pandemic on influenza vaccination rates 2) To describe self-reported complications from influenza experienced by individuals with different cardiovascular conditions during the 6-month study period, as well as differences in complications by vaccination status 3) To examine differences in wearable data (e.g., sleep, steps, heart rate) between individuals who experience self-reported influenza and those who do not, as well as differences in wearable data between cardiovascular conditions
Endpoints	Primary endpoint ● Self-reported influenza vaccination rates Secondary endpoints ● Engagement with interventions (i.e., clicking, opening, completing) ● Self-reported vaccine drivers/barriers, and vaccine knowledge Exploratory endpoints ● Self-reported impact of COVID-19 on influenza vaccination behavior ● Self-reported complications from influenza ● Passively collected wearable data (e.g., sleep, steps, heart rate)

Patient Population	Inclusion Criteria: ● Age 18 years or older ● Resides in the U.S. ● Speaks, reads, and understands English ● Has self-reported being diagnosed with any of the following cardiac conditions below in their Achievement profile: ○ Atrial Fibrillation or Afib ○ Abnormal or irregular heart rhythm, other arrhythmic heart disease ○ Cardiac arrest, or heart attack (myocardial infarction) ○ Coronary heart disease like a heart blockage, treated with medications, a stent in the heart, or sometimes bypass surgery ○ Heart failure, like congestive heart failure ○ Stroke or cerebrovascular accident (CVA) Exclusion Criteria: ● Participated in Step 1, Part 2 semi-structured interviews used to obtain feedback on the intervention messages

1. Introduction

1.1. Overview of Therapy Area

Influenza impacts approximately 5-20% of the population of the United States annually, resulting in significant economic impact and public health burden (Molinari et al., 2007). For people with cardiovascular conditions, influenza can be particularly burdensome, thus they are considered a high-risk group (CDC, 2019). Vaccination for influenza remains the most effective primary prevention method against influenza, with effectiveness ranging from 38-48% in the past few years (Centers for Disease Control and Prevention (CDC), 2018; Dos Santos, Tahrat, & Bekkat-Berkani, 2018; Doyle, 2019; Jackson et al., 2017; Rolfes et al., 2019). The CDC reports that the vaccination rate in the 2018-2019 season was 47.9% for individuals 18-64 years of age who have high risk conditions such as cardiovascular conditions (CDC, 2019). While this is higher than the rate of 36.4% in same age individuals without high risk conditions, it is far below the 70% national vaccination rate goal (Healthy People 2020, 2019). Given the increased burden that influenza represents for people with high risk conditions, even small improvements in vaccination rates could result in significant impact and provide benefit to patients, healthcare providers, and insurance payors (Molinari et al., 2007).

1.2. Study Rationale

To date, there are no large-scale RCTs on digital interventions for increasing vaccination rates in people with cardiovascular conditions. One observational study has demonstrated the potential effectiveness of general messaging and incentives via a health-related app to increase vaccine uptake in the general Canadian population (Dale, White, Mitchell, & Faulkner, 2019), suggesting this kind of intervention could be effective with people with cardiovascular conditions. In a separate study, a large randomized controlled trial (RCT) using digital messaging with incentives to vaccinate was found to be effective in increasing vaccination rates in a general population of adults in the United States (Lee et al., 2020). Of particular interest is a digital RCT in a sample of individuals with diabetes, a population with increased risk of influenza-related complications, that used digital messaging and was found to be effective in increasing vaccination rates (Samson, et al., 2020). An additional study of individuals with diabetes that was a collaboration between Sanofi Pasteur and Evidation also demonstrated the impact of influenza and related complications on data retrieved from wearables; showing that people who developed influenza engaged in less activity around the time of diagnosis and recorded an increased heart rate, a unique passive marker of infection (Samson et al., 2019). These studies all suggest that the development of a digital intervention targeted to individuals with cardiovascular conditions could be beneficial in increasing vaccination rates.

1.3. Intervention Overview

The digital intervention messages were developed using a 3-part approach: 1) a quantitative assessment of more than 800 patient perspectives for people with cardiovascular disorders, assessing their behaviors, thoughts, and beliefs surrounding vaccination; 2) semi-structured interviews with approximately 25 patients who had cardiovascular diseases to gather their perspectives and feedback on proposed intervention messages; and 3) an expert panel of cardiologists, behavioral scientists, and vaccine policy experts for expert input on content and accuracy of scientific information provided. This approach to intervention development was consistent with the Patient Centered Outcomes Research Institute (PCORI) recommendation for developing interventions that increase participant recruitment and retention, improve patient outcomes, and increase research validity and relevance to the real world (Frank, Basch, & Selby, 2014). The intervention messages provide informational content on the influenza vaccine (sourced from the Centers for Disease Control and Prevention and the American Heart Association), specific information about influenza and cardiovascular disorders, and behavioral prompts (e.g., reminders) surrounding influenza vaccination behaviors.

2. Study Objectives

2.1. Primary Objective

- To determine the effectiveness of a digital intervention designed to increase influenza vaccination rates in individuals with cardiovascular diagnoses (CV diagnoses) by examining differences in self-reported influenza vaccination rates between individuals with cardiovascular disease who receive a targeted digital intervention (CVD-I) aimed at increasing influenza vaccination and those with CV diagnoses who received no intervention (CVD-C) by the end of the study period.

2.2. Secondary Objectives

- To examine differences in vaccination rates between individuals in CVD-I who engaged with different numbers of intervention messages, and changes in self-reported vaccination rates following intervention messages
- To describe levels of engagement with the intervention messages and perceptions of the intervention messages within the CVD-I group
- To examine predictors of vaccination status, including cardiovascular condition type, vaccine drivers/barriers, and vaccine knowledge, across diagnoses and within CVD-I and CVD-C groups

2.3 Exploratory Objectives

- To examine the potential impact of COVID-19 pandemic on vaccination rates

- To describe self-reported complications from influenza experienced by individuals with different cardiovascular conditions during the 6-month study period, as well as differences in complications by vaccination status
- To examine differences in wearable data (e.g., sleep, steps, heart rate) between individuals who experience self-reported influenza and those who do not, as well as differences in wearable data between cardiovascular conditions

3. Study Design

3.1. Overall Design

- A 6-month prospective, digital randomized controlled trial targeting approximately 35,000 individuals to evaluate the effectiveness of an influenza vaccination intervention during influenza season for people with cardiovascular conditions
- Two study arms: cardiovascular disorders digital intervention arm (CVD-I) & cardiovascular disorders without digital intervention arm (control: CVD-C)

4. Study Endpoints

4.1. Primary Endpoint

The primary endpoint in this study is to examine differences in self-reported influenza vaccination rates between individuals with cardiovascular disease who receive a targeted digital intervention (CVD-I) aimed at increasing influenza vaccination and those with cardiovascular disease who received no intervention (CVD-C).

4.2. Secondary Endpoint

The secondary endpoints in this study are:
- To examine predictors of vaccination status, including cardiovascular condition type, vaccine drivers/barriers, and vaccine knowledge, across and between CVD-I and CVD-C.
- Engagement with interventions, including clicking, opening, or completing the intervention messages

4.3. Exploratory Endpoints

The exploratory endpoints in this study include:
- To describe the self-reported impact of the COVID-19 pandemic on influenza vaccination behavior

- To describe self-reported complications from influenza experienced by individuals with different cardiovascular conditions during the 6-month study period, as well as differences in complications by vaccination status.
- To examine differences in wearable data (i.e., sleep, steps, heart rate) between individuals who experience influenza and those who do not, as well as differences in wearable data between cardiovascular conditions.

5. Study Population

5.1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
● Age 18 years or older ● Resides in the U.S. ● Speaks, reads, and understands English ● Has self-reported being diagnosed with any of the following cardiac conditions below in their Achievement profile: o Atrial Fibrillation or Afib o Abnormal or irregular heart rhythm, other arrhythmic heart disease o Cardiac arrest, or heart attack (myocardial infarction) o Coronary heart disease like a heart blockage, treated with medications, a stent in the heart, or sometimes bypass surgery o Heart failure, like congestive heart failure o Stroke or cerebrovascular accident (CVA)	● Participated in Step 1, Part 2 semi-structured interviews used to obtain feedback on the intervention messages.

5.2. Recruitment Methods

Achievement, a product of Evidation Health, is an online platform where people can connect their digital health tools, including wearable activity trackers and fitness apps. Achievement

members agree to being contacted with study opportunities when they create an Achievement account. Evidation Health will leverage Achievement for recruitment, and will use an online strategy and study platform to develop a target list of participants, verify eligibility, and enroll participants into this study.

A set of existing Achievement members who have previously self-reported to meeting the inclusion criteria will be tagged for study inclusion, termed "participants" from here on. Since participants will be blinded to their study participation status, participants will not be asked to take any action to enroll in the study. In order to identify a target list of participants, Evidation Health will leverage already permissioned information from Achievement members, including data on their cardiovascular diagnoses, age, sex/gender, race/ethnicity, and country of residence. These participants will be randomized using block randomization into CVD-Intervention or CVD-Control prior to being offered the opportunity to complete any study activities. Randomization will ensure that the groups are representative of the general Achievement population with cardiovascular disease. Efforts will be made to target individuals for enrollment who identify as being of a race/ethnicity that is something other than non-Hispanic White, as well as representative in sex/gender. Participants will be sent offers via the Achievement platform to complete study activities. Participants can complete any number of survey activities (demographics, baseline, 3-month survey, and/or 6-month survey, intervention messages); completion of intervention activities will not be required for enrollment for the CVD-I group.

6. Study Procedures

6.1. Study Enrollment

Participants will be sent offers on the Achievement Studies Platform to complete study activities. Participants can complete any number of survey activities (baseline, 3-month survey, and/or 6-month survey, intervention messages); completion of intervention activities will not be required for enrollment for the CVD-I group.

6.2. Informed Consent

We will request that informed consent is exempt for this study for the following reasons:

- Participation in this study involves no more than minimal risk to the privacy of individuals.
- Given the nature of the study, which aims to measure influenza vaccination rates in a real-world setting, priming the participants with a consent form will likely alter the perception of the interventions and may impact how individuals respond to the study assessments, potentially biasing the results and limiting the generalizability of the findings. For this reason, this study could not be practically carried out without the waiver of informed consent.
- At the beginning of each questionnaire, participants will be notified on how their survey responses and behavioral data will be used for research purposes via a Data Usage & Permissions Agreement.

6.3. Study Steps

Participants will be sent an offer to complete a survey at baseline, 3 months, and 6 months. A separate demographic and medical history survey will remain available for participants to complete throughout the study. Additional information on study experiences and intervention feedback will be gathered in the 6-month survey for those in the CVD-I group. Data from an activity tracker will be collected if one is already connected to the participant's Achievement account, consistent with their completion of the Data Usage & Permissions Agreement. Activity tracker data will be collected retrospectively and prospectively. Participants in the CVD-I arm only will be sent intervention messages on predetermined days for the duration of the 6-month study intervention period. At the end of the intervention period, individuals who completed a data usage and permissions agreement as a part of the surveys will be informed via email that the survey information they contributed was for a research study investigating influenza vaccination behavior in people with cardiovascular conditions.

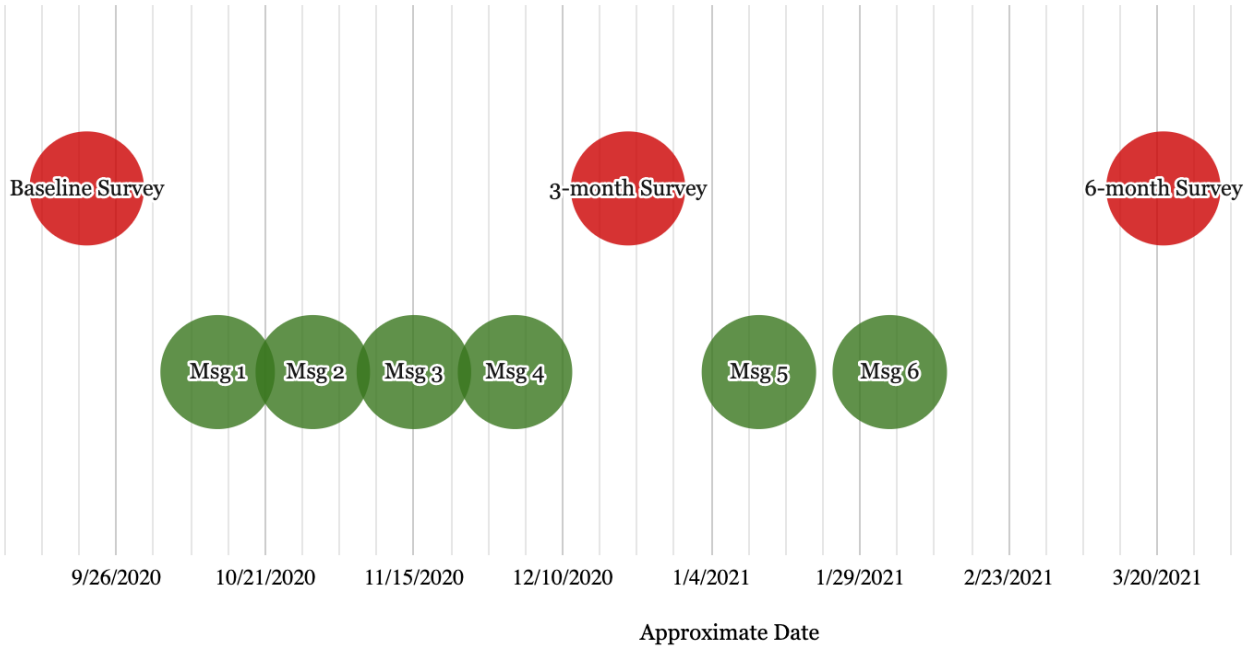
6.4. Study Compliance

Evidation study staff will track whether participants are completing study-related tasks throughout the study. Participants who do not complete study activities may be contacted by email, text message, or push notifications with reminders to complete activities, within a time window that is appropriate to the specific task, but will remain in the study sample regardless of whether they submit data in a timely manner.

6.5. Compensation

Participants in both arms will be compensated for completing surveys. Participants in the CVD-I will be compensated minimally for the completion of intervention tasks (e.g., completing short quizzes, scheduling a date for their influenza vaccine, reading an article to learn more about the flu, the flu shot, and their cardiovascular conditions), to avoid incentivizing vaccination status unequally between the two arms. The compensation amounts will be detailed in the Data Usage & Permissions Agreements at the beginning of each survey for CVD-I and CVD-C arms, and in the offer to complete the intervention messages for the CVD-I arm. All compensation will be awarded in Achievement Points, of which 100 points is equivalent to $0.10. Points can be redeemed for monetary compensation or donated to charitable organizations. The following compensation will be awarded: 50 points per intervention message completed, 3 points per optional informational email requested, and 300 points per survey completed. The maximum number of points possible is 1,518 points, which could be redeemed for approximately $1.52.

6.6. Study Flow Diagram



Note. Dates are approximate.

7. Data Types and Outcomes

- Data from self-reported survey:
  - Demographics
  - Medical history
  - Health behaviors
  - Healthcare utilization
  - Influenza vaccination status, experience, and complications
  - COVID-19 experiences
  - Vaccine attitudes and barriers
  - Influenza risks and healthcare provider role
  - Experience and perceptions of intervention materials (CVD-I only)
- Data from engagement with interventions (CVD-I only)
  - For example, clicks, dismissals, or completions of interventions
- Data from Achievement Profile
  - Activity data generated by wearables (e.g., heart rate, sleep, step data), from 12 months before participation and 12 months after participation (if available)

	Source	Retrospective	Demographics	Baseline	Month 3	Month 6

		12 months before to 12 months after	Survey			
Self-reported data						
Demographics	Survey		X			
Medical history	Survey		X			
Health behavior history & influenza vaccination	Survey		X			
Healthcare utilization	Survey			X	X	X
Influenza vaccination status	Survey			X	X	X
Influenza experience & complications	Survey			X	X	X
COVID-19 experiences & perceptions	Survey			X	X	X
Vaccine drivers & barriers	Survey			X	X	X
Influenza risks & healthcare provider role	Survey			X	X	X
Experience and perceptions of intervention materials	Survey					X (CVD-I only)
Engagement with interventions	Achievement website/app and Survey Monkey		[----------continuous----------] (CVD-I only)			
Activity tracker data						
Steps	[e.g. Fitbit, Garmin]	X	[----------continuous----------]			
Sleep	[e.g. Fitbit, Beddit]	X	[----------continuous----------]			
Heart rate	[e.g. Fitbit, Apple]	X	[----------continuous----------]			

8. Statistical Considerations

8.1. Sample Size Justification

We determined sample size for a two-arm interventional statistical superiority study design with vaccination rates as the primary outcome of interest (Zhong 2009). Studies on the impact of messaging and reminders to improve influenza vaccination rates show a range of effect sizes from 2.5 - 3.5% (Nehme et al., 2019, Hurley et al., 2018). As noted earlier, CDC reported vaccination rates are 47.9% for adults between the ages of 18 - 65.

Given these a-priori assumptions, we assumed different baseline vaccination rates of 35%, 50% and 60%, and then computed the sample size needed to detect an increase in vaccination rate of 2%, 3% and 4% respectively. Sample size for the difference in proportion is determined by (Zhong, 2009):

$$N = \frac{1}{2}\left(\frac{z_{\alpha/2} + z_{\beta}}{arcsin\sqrt{p} - arcsin\sqrt{p_0)}}\right)^2$$

Where:
$Z_{\alpha/2}$ and Z_{β} refer to the z critical values for a type I and II error of 0.05 and 0.2 respectively,
p_0 and p are the baseline proportion and the new hypothesized proportion respectively, and
N is the total sample size, assuming a 1:1 ratio of intervention to control

Baseline vaccination rate	Hypothesized vaccination rate	Hypothesized effect size	Hypothesized Cohen's h	Sample size
35.0%	37.0%	2.0%	4.2%	18080
50.0%	52.0%	2.0%	4.0%	19610
60.0%	62.0%	2.0%	4.1%	18668
35.0%	38.0%	3.0%	6.2%	8080
50.0%	53.0%	3.0%	6.0%	8710
60.0%	63.0%	3.0%	6.2%	8256
35.0%	39.0%	4.0%	8.3%	4570
50.0%	54.0%	4.0%	8.0%	4894
60.0%	64.0%	4.0%	8.2%	4618

In the above table, for each baseline rate and hypothesized rate increase (and associated Cohen's h), we show the estimated total sample size needed for each assumption of baseline vaccination

rate and effect size. We note that within each hypothesized effect size, changing assumptions about baseline vaccination rates do not substantially alter the sample size.

Based on this, we believe that a 3% effect size is a reasonable assumption and that a sample size of approximately 8000 participants will be needed to detect this difference with a type I error rate of 0.05 and a presumed power of 0.80. A participation dropoff of 67% has been observed for digital interventions for increasing influenza vaccination (i.e., Samson et al., 2020). Assuming between 67% to 75% dropoff for this study, we estimate that between 24,000 - 35,000 participants will need to be recruited and randomized for this study. Based on these calculations, we plan to recruit approximately 35,000 participants.

8.2. Description of Analytical Plan

8.2.1. Baseline Descriptive Statistics

Descriptive statistics (e.g., mean, standard deviation, frequency and percentage) of study participants will be reported for demographic variables (e.g., age, gender, education, income) and patient reported outcomes (e.g., vaccination rates). To confirm that block randomization is successful, we will compare the intervention to control groups in terms of baseline demographics, vaccine drivers/barriers, and vaccine knowledge for each of the block groups described earlier.

8.2.2. Analysis of Primary Endpoint

An intention to treat analysis will be conducted of the primary outcomes for the study. Assuming that a descriptive comparison of the intervention to control group does not demonstrate statistically significant differences in terms of demographics, vaccine drivers/barriers, or vaccine knowledge, we will report on the relative rate of influenza vaccination for the intervention group compared to the control group. We will also conduct logistic regression modeling of influenza vaccination as follows:

$$logit(Y) = \beta_0 + \beta_1 M + \sum_j \beta_j \alpha_j + \varepsilon$$

Where:
logit(Y) = ln(Y/1-Y) for the binary variable designation of influenza vaccination status
M = the binary designation for Intervention (messaging) vs Control (no messaging)
α_j = the baseline covariates measured in the study (e.g. demographics, vaccine drivers/barriers or knowledge)
ε = the error term of the regression.

For the logistic regression model the p-values associated with each of the β parameter estimates will be reported.

8.2.3. Analysis of Secondary Endpoint

To examine differences in vaccination rates between individuals in the CVD-I group and its relationship to engagement with intervention messages, we will model:

$$logit(Y) = \beta_0 + \beta_1 M + \sum_j \beta_j \alpha_j + \varepsilon$$

Where:
logit(Y) = ln(Y/1-Y) for the binary variable designation of influenza status
M = the number of engaged messages (ordinal variable 0, 1, 2, 3, 4, 5, 6)
α_j = the baseline covariates measured in the study (e.g. demographics, vaccine drivers/barriers, or knowledge)

To examine predictors of vaccination status, including cardiovascular condition type, vaccine drivers/barriers, and vaccine knowledge, across CVD-I and CVD-C we will construct the model:

$$logit(Y) = \beta_0 + \beta_1 P + \sum_j \beta_j \alpha_j + \varepsilon$$

Where:
logit(Y) = ln(Y/1-Y) for the binary variable designation of influenza status
C_i = the binary designation Cardiovascular Condition as described earlier
P = the predictor of interest (e.g. cardiovascular condition, vaccine drivers/barriers, vaccine knowledge index)
α_j = the baseline covariates measured in the study (e.g. demographics, vaccine drivers/barriers, or knowledge)
ε = the error term of the regression.

To examine predictors of vaccination status, including cardiovascular condition type, vaccine drivers/barriers, and vaccine knowledge, within CVD-I or CVD-C we will construct the model:

$$logit(Y) = \beta_0 + \beta_1 M + \beta_2 P + \sum_j \beta_j \alpha_j + \varepsilon$$

Where:
logit(Y) = ln(Y/1-Y) for the binary variable designation of influenza status
M = the messaging group being examined (either Intervention or Control)
P = the predictor of interest (e.g. cardiovascular condition, vaccine drivers/barriers, vaccine knowledge index)
α_j = the baseline covariates measured in the study (e.g. demographics, vaccine drivers/barriers, or knowledge)
ε = the error term of the regression.

8.2.4. Exploratory Analyses

To examine the potential impact of COVID-19 on vaccination rates, we will add a term to the model used in the primary analysis model:

$$logit(Y) = \beta_0 + \beta_1 M + \sum_j \beta_j \alpha_j + \beta_c c + \beta_i M * c + \varepsilon$$

Where the additional term *c* is the Covid-19 status (1 if diagnosed with COVID-19, 0 if not) and the parameter estimate for the interaction term, β_i will be reported. Similarly, we can also evaluate the effect of COVID-19 attitudes towards influenza vaccination rates. In this case, the term *c* would represent COVID-19 attitudes (1 if the participant reports more likely to vaccinate, 0 if the person does not).

To describe self-reported complications from influenza experienced by individuals with different cardiovascular conditions during the 6-month study period, as well as differences in complications by vaccination status, we will aggregate rates of self-reported complications by cardiovascular conditions, as well as by vaccination status.

To examine differences in wearable data (i.e., sleep, steps, heart rate) between individuals who experience influenza and those who do not, as well as differences in wearable data between cardiovascular conditions, we will aggregate day-level wearable data over the entire study period based on influenza status, as well as by cardiovascular condition.

Between-group comparisons of the outcomes described above (e.g. self reported complications or mean daily steps) will be conducted with Student's t-tests or the non-parametric Mann-Whitney U test when appropriate, with correction for multiple testing using the Benjamini-Hochberg approach for False Discovery Rate correction.

9. Data Security and Confidentiality

All identifiable information about participants, their medical conditions, and other study data will be secured by Evidation Health in accordance with all applicable local and state laws, regulations, and IRB policies regarding collection and distribution of participant information.

Data will be transmitted using secure encrypted protocols and stored on encrypted disks on secure and hardened servers. Administrative access to these servers is limited to only the necessary IT staff at Evidation Health. Survey data may be stored for a minimum of 3 years, consistent with contract and applicable law.

Personally Identifiable Information (PII) is only accessible to a restricted set of individuals, and is only used to distribute study material and for participant support purposes. PII will not be disclosed unless required by regulatory agencies or the IRB in instances consistent with applicable law. Limited Achievement clinical, research and technical team members at Evidation Health only have access to Coded Study Data where all PII is replaced with random unique identifiers. Coded Study Data may also be transferred to external research partners, including Sanofi Pasteur, in accordance with IRB approved uses.

10. Risks and Benefits

10.1. Potential Risks Associated with the Study

This is a minimal risk study that does not involve any risk beyond what a person would experience in their daily life. While we strive to protect the privacy of personal information and implement appropriate safeguards, complete security cannot be guaranteed. There is the potential risk of loss of privacy associated with this study if another person sees the participant's survey responses on their phone or computer screen. Participants may decline to answer certain survey questions.

10.2. Potential Benefits Associated with the Study

Participants of this study will likely not receive any direct benefit from the proposed research; however, society and investigators will benefit from the knowledge gained. This information may contribute to public health and scientific efforts related to vaccination and the prevention of disease for people with cardiovascular disorders. This information may help researchers develop further interventions to increase influenza vaccination.

10.3. Adverse Events

Adverse events will not be actively collected because no pharmaceutical product or medical treatment will be provided or evaluated in this study. Spontaneously reported adverse events received by Evidation Health will be recorded per Evidation Health's Standard Operating Procedures.

Any pharmacovigilance data pertaining to a Sanofi product potentially collected will be notified by Evidation Health to Sanofi Pasteur Pharmacovigilance, who is working with Evidation on this research project, through email (CL-CPV-Receipt@sanofi.com), within 1 (one) working day for serious adverse events.

A "serious adverse event (SAE)" is defined as any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening, (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or results in prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Appendix

Please see attached appendix for examples of the intervention messages.

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