Influenza Vaccination Digital Interventions for People living with Diabetes

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Study Protocol: Influenza Vaccination Digital Interventions for People living with Diabetes

Principal Investigator:
Luca Foschini, PhD Co-
Principal Investigator: Jessie L.
Juusola, PhD

Sub-Investigators:
Shefali Kumar, MPH
Caroline Tai, PhD

Sponsor: Evidation Health

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Introduction

Overview of Therapy Area

It is estimated that each year 5-20% of the U.S. population have an influenza infection (also known as flu) (Molinari, 2007). Influenza may lead to adverse outcomes such as primary influenza pneumonia, secondary bacterial infection, and an increased risk of acute coronary syndromes (Nicholson, 2003). The most effective way to reduce the risk of developing influenza is to get vaccinated. Influenza vaccination is also one of the most effective chronic care interventions; for example, it has shown to be an effective secondary prevention against myocardial infarction (MacIntyre, 2016). However in recent years, influenza vaccination rates for adults in the U.S. have remained suboptimal at approximately 40-50% (CDC, 2017).

Compared to the general population, individuals with diabetes who get influenza have a greater risk of developing adverse outcomes such as pneumonia, bronchitis, sinus infection and ear infections, and can develop diabetes-specific adverse outcomes such as diabetic ketoacidosis (CDC, 2017). The Centers for Disease Control and Prevention recommends annual influenza vaccination for all people living with diabetes, however,

similar to overall vaccinations rates for adults in the U.S., vaccination rates for people living with diabetes also has remained suboptimal.

Overview of Digital Intervention

In this study, we aim to examine two different digital interventions: the *Diabetes Digital Intervention* and the *General Digital Intervention*. Both interventions will be driven via a digital campaign, which will provide interactive ways (e.g., videos, infographics, quizzes) for individuals to learn about influenza and related complications, and the importance of influenza vaccination. The *Diabetes Digital Intervention* will be tailored to people living with diabetes and will include an intervention that highlights the importance of influenza vaccination for this specific patient population. The *General Digital Intervention* will provide generic influenza vaccination interventions that can be applicable to any adult who should receive influenza vaccination.

Objectives and Overall Study Design

The overall objective of this 3-arm, 6-month long prospective randomized controlled study is to assess and quantify the impact of digital interventions to increase vaccination rates and vaccination-related outcomes in a connected population with selfreported diabetes. The digital intervention will be delivered via a campaign sent to participants, with interventions varying with each study arm. Participants will be blinded to study participation status.

This study will consist of the following populations:

- Population 1 (P1): Individuals with self-reported diabetes
- Population 2 (P2): Individuals without self-reported diabetes who are similar to P1 based on demographics and activity tracker data
- Population 3 (P3): Individuals without self-reported diabetes and are not in P2 based on demographics and activity tracker data, but are similar to P1 with regards to age and gender distribution

The three study arms are described below:

- Arm 1: Individuals in P1 who receive the *Diabetes Digital Intervention*
- Arm 2: Individuals in P2 and P3 who receive the *Generic Digital Intervention*
- Arm 3: Individuals in P1, P2, and P3 who do not receive any digital intervention

Based on these three populations and three arms, we will examine the following cohorts in this study:

		Population		
		P1: Individuals with selfreported diabetes	P2: Individuals without selfreported diabetes who are similar to P1 based on demographics and activity tracker data	Population 3 (P3): Individuals without selfreported diabetes and are not in P2, but are similar to P1 with regards to age and gender distribution
Arm	Arm 1: Diabetes Digital Intervention	Cohort 1	NA	NA
	Arm 2: Generic Digital Intervention	NA	Cohort 3	Cohort 5
	Arm 3: No Influenza vaccination intervention	Cohort 2	Cohort 4	Cohort 6

Patient Eligibility

Inclusion Criteria	Exclusion Criteria
• Ages 18 and older • Lives in the U.S.	• < 18 years old • Does not live in the U.S.

Achievement, a proprietary asset of Evidation Health, is an online program where people can connect their digital health tools, including wearable activity trackers and fitness apps. Existing Achievement members are typically ages 18 and older and live in the U.S. We will limit inclusion in the study sample to those who meet that criteria based on their Achievement registration information, and we will only include in analysis those who confirm these characteristics in study questionnaires.

Subject Recruitment, Enrollment and Study Procedures

Achievement members agree to being contacted with study opportunities when they create an Achievement account. Evidation Health will leverage Achievement for this study.

A set of existing Achievement members who meet 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. Participants will be randomized to one of the three study arms relevant to them, based on which population they are in. Based on which arm the participant is randomized to, they may receive the digital intervention throughout the study period.

All participants will be invited to complete a baseline assessment (SeptemberOctober). The baseline assessment will include questions on demographics, health status, diabetes history, complications and treatment (if applicable), influenza and influenza vaccination history, perception of influenza vaccination, role of their health care provider in influenza vaccination decisions, and overall healthcare utilization.

Mid-way through the influenza season (early- to mid-December), participants will be asked to complete an online mid-study assessment to assess whether they received an influenza vaccination or had influenza yet this season, and influenza experience for those who did have influenza. Information about demographics, health status, perception of influenza vaccinations, role of their health care provider in influenza vaccination decisions, and overall healthcare utilization will also be collected.

At the end of influenza season (mid-March), participants will be asked to complete an online study-end assessment to assess whether they received influenza vaccination or had influenza this season, influenza experience for those who did have influenza, perception of influenza vaccination, and role of their health care provider in influenza vaccination decisions. Demographics, health status, and overall healthcare utilization will also be collected. Cohorts 1, 3 and 5 (individuals who received either the *Diabetes Digital Intervention* or the *Generic Digital Intervention*) will also be asked about their reactions to the intervention campaign.

Participants will earn Achievement points, which can be redeemed for monetary rewards (in USD), for completing the questionnaires. Participants who do not complete questionnaires may be contacted by email, text message, push notification, and/or phone call with reminders to complete questionnaires. All submitted data will be included in the study analysis set, regardless of completion of previous or subsequent questionnaires.

Informed Consent

We 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.

At the beginning of each questionnaire, participants will be notified on how their survey responses and behavioral data will be used for research purposes.

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 local and state laws, regulations, and IRB policies regarding collection and distribution of patient information. Data will be transmitted using Transport Layer Security (TLS) 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.

Personally Identifiable Information (PII) is only accessible to a restricted set of individuals, and is only used to distribute invention and study material and for participant support purposes. Researchers 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 in accordance with IRB approved uses.

Primary, Secondary and Supplemental Outcomes

Outcome	**Description**
Primary	Difference in self-reported influenza vaccination rates between Cohort 1 and Cohort 2
Secondary	Secondary endpoints will include • Difference in differences in self-reported influenza vaccination rates between Cohort 1 and 2 as compared to Cohort 3 and 4 • Impact of when intervention is sent (when participant is wearing an activity tracker vs. when participant is not wearing an activity tracker) on self-reported influenza vaccination rates

Supplemental	Potential supplemental endpoints may include • Difference in self-reported influenza vaccination rates from previous year to study year, by cohort • Difference in self-reported influenza vaccination rates between Cohort 3 and Cohort 4 • Difference in self-reported influenza vaccination rates between Cohort 5 and Cohort 6 • Agreement of influenza vaccination predictive score and selfreported influenza vaccination • Whether specific interventions changes participants' mindset towards influenza vaccination • Self-reported impact of influenza (if participant develops influenza, how long influenza lasted, healthcare utilization, etc.) o Disease modulation (if participant develops influenza, influenza symptom severity) • Role of health care provider in influenza vaccination decisions • Difference in activity tracker-based behavioral characteristics (as measured by tracker use, steps, sleep and heart rate data) between various subgroups of the population

Analytic Plan

Descriptive analyses will report summary statistics such as mean, standard deviation, and percentage of all baseline characteristics by cohort. Baseline characteristics will be derived from data collected in the assessments such as demographics, health status, comorbidities, and overall healthcare utilization. Any differences between compared cohorts (Cohorts 1 vs. 2, Cohorts 3 vs. 4, and Cohorts 5 vs. 6) will be evaluated using the appropriate statistical test based on format and distribution of the variable (i.e., chi-square, t-test, Mann Whitney U test).

Intent-to-treat analysis will be conducted for primary, secondary and supplemental outcomes. The primary analysis will test for a difference in proportion of self-reported influenza vaccination during the 2018-2019 influenza season between Cohort 1 and Cohort 2 using chi-square tests. Secondary analyses will be evaluated as a difference in differences comparison where the difference in proportions of self-reported influenza vaccination between Cohort 1 and Cohort 2 will be compared to the difference in proportions of self-reported influenza vaccination between Cohort 3 and Cohort 4 using t-tests and regression

models that test the statistical significance of an interaction between arm and population. Effect modification by activity tracker (intervention messages sent when wearing tracker vs. when not wearing tracker) will be evaluated as an additional interaction term in the regression model or by stratification, as appropriate. Any potentially confounding variables found to be unbalanced between compared cohorts will be adjusted for as covariates in regression models.

Supplemental analyses will evaluate differences in the outcomes between compared cohorts and will utilize t-test, ANOVA, chi-square test, or McNemar's (chisquare test for paired data) test based on format and distribution of outcome. Difference in difference comparisons for supplemental outcomes will use t-tests or regression models, similar to secondary analyses.

Exploratory analyses will also be performed on activity data. We will reimplement all main analyses on sub-cohorts defined by behavioral features. e.g., high vs. low average physical activity (measured as daily step counts), high vs low sleep quality (measured as average sleep efficiency), high vs. low fitness level (measured as resting HR). Time-series analyses of activity data may be performed around specific index events (e.g., day when intervention is received).

Sample Size

We will aim to include 60,000-90,000 participants in this study. The study is powered to show effect in the primary outcome of difference in vaccination rate for individuals with diabetes who receive a diabetes-related influenza vaccination intervention (Cohort 1) and those who receive no influenza vaccination intervention (Cohort 2). We estimate a difference of 2.7 percentage points as a meaningful and reasonable effect size, based on 2 similar studies, described below.

One unpublished study run by Evidation Health tested the impact of a messaging intervention encouraging vaccination delivered by push notification through the wellness platform of a large national health insurer. The observed increase in vaccination due to the messaging was 1.1 percentage points. We believe this constitutes a lower bound to the lift expected in the current study for two reasons: 1) vaccination increase was measured in December, thus not capturing the full duration of the influenza vaccination period and 2) vaccination rate was measured via claims data, which is expected to have a 45% unreported vaccination rate.

A second recent study (Dale, 2018), tested the impact of a geographicallylocalized push notification encouraging vaccination to members of a wellness platform. This intervention was estimated to increase vaccination rate by 5.4 percentage points. The study featured a more powerful intervention than the one that will be tested here (e.g., intervention messages were sent when participant was near a participating pharmacy), therefore we believe it may be an upper bound to what we can expect in our study. If we assume an effect size at least double study 1 but less than study 2, (i.e., 2.7 percentage points), then we need 4,043 individuals for each of the two arms of P1, for a total of 8,086 study participants across the two arms.

We will label a larger population for study inclusion than determined by the powering calculations in order to account for realistic questionnaire participation rates. Assuming approximately 30-40% of individuals tagged as participants will complete the mid-study or study-end assessment, we would need to include approximately 20,00030,000 individuals with diabetes (P1) as participants in the study. We will label similar numbers for P2 and P3, for a total of at least 60,000 participants in this study.

Risks and Benefits

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. It is an exploratory study that will not provide any form of medical advice or medical intervention other than what is routine to standard of care (i.e., recommendation for annual influenza vaccination). 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.

Adverse Events

Given that there are no pharmaceutical products administered as part of this study, there is no potential to find any pharmacovigilance data thereof associated with the use of influenza vaccines.

Any pharmacovigilance data 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.

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 lifethreatening 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.

Potential Benefits Associated with the Study

During this study, participants may develop a better understanding of their own health and may be encouraged to get their influenza shot, which has been shown to be the most effective method for influenza prevention. In addition, participants will be contributing to the understanding of how individuals can be motivated and encouraged to get their influenza vaccination.

References

1. Centers for Disease Control and Prevention, Vaccination Coverage, United States, 2016-17 Influenza Season. https://www.cdc.gov/flu/fluvaxview/coverage1617estimates.htm
2. Centers for Disease Control and Prevention, Flu and People with Diabetes. https://www.cdc.gov/flu/diabetes/index.htm
3. Dale LP, White L, Mitchell M, et al. Smartphone app uses loyalty point incentives and push notifications to encourage influenza vaccine uptake. Vaccine 2018.
4. MacIntyre CR, Mahimbo A, Moa AM, Barnes M. Influenza vaccine as a coronary intervention for prevention of myocardial infarction. Heart. 2016 Dec 15;102(24):1953-1956.
5. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine. 2007 Jun 28;25(27):5086-96.
6. Nicholson KG, Wood JM, Zambon M. Influenza. Lancet 2003;362:1733–45.