BE IMMUNE: Behavioral Economics to IMprove and Motivate vaccination Using Nudges through the EHR

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NCT#06057727

Study Protocol v5 August 2024

Approved: 10/7/2024

Outline

1. Abstract

Many older adults are at risk of illness, hospitalization, and death from vaccine-preventable diseases. More than half of older adults in the United States are not vaccinated for flu which has remained relatively constant over the past decade, and there are racial, ethnic, and socioeconomic disparities in care. In this study, we will evaluate personalized nudges to clinicians and patients to help increase flu vaccination rates during primary care visits among older adults at three distinct health systems, with a particular focus on population subgroups at high risk for vaccine noncompletion. In a partnership between Penn Medicine and University of Washington (UW) Medicine, this will be a 6-month, multisite, cluster randomized, pragmatic trial with an additional intensification arm for high-risk patients. We will also perform a 6-month replication trial at Lancaster General Health.

2. Overall objectives

The objectives of the study are to:

1) To conduct a 6-month, multisite, cluster randomized, pragmatic trial to evaluate the effectiveness of personalized nudges to clinicians and patients relative to control to improve flu vaccine completion among older adults.
2) To evaluate the effectiveness of an additional, intensification nudge intervention on reducing disparities in flu vaccine completion among high-risk subgroups.
3) To evaluate heterogeneity in treatment effect across clinician, patient, and practice characteristics to further tailor approaches in future intervention design.

3. Aims

3.1 Primary Outcome

The primary outcome is flu vaccination completion during the first eligible primary care visit.

3.3 Secondary outcome

The secondary outcome is flu vaccination completion within 3 months after the first eligible primary care visit.

4. Background

Older adults are at risk of serious illness and hospitalization from vaccine-preventable disease.[1,2] The low vaccination rates have remained relatively stable over the last decade, indicating an urgent need for novel, scalable interventions to increase vaccination rates.[3] Further, significant disparities exist relative to who receives a vaccination.[4] Over 90% of clinicians use the electronic health record to facilitate decision making.[5] Prior work has demonstrated that EHR-based nudges can increase vaccination ordering rates, cancer screening rates, and statin prescribing.[6-9] Building upon our prior work, we propose to use analytical methods to identify older adults at high-risk of flu vaccination non-participation, assess the feasibility of using a set of EHR-based nudge interventions at two primary sites (Penn Medicine and UW Medicine) to improve flu vaccination among older adults, especially those in high-risk groups. We then plan to replicate these findings in a third site, Lancaster General Health.

5. Study design

5.1 Design

This study will be a multisite, cluster randomized, pragmatic trial to evaluate the effectiveness of personalized nudges to clinicians and patients, relative to a control, to increase flu vaccination rates among older adults in accordance with CDC guidelines. This will include clinician and patient level nudge interventions, with additional, intensified nudge interventions for patients identified as high risk for not receiving a flu vaccine.

This cluster randomized trial will randomly assign primary care clinics in a 2:1 ratio to either a nudge interventions or control arm using a covariate-constrained randomization.[10] The intervention arm consists of a multi-component nudge intervention for patients and primary care providers (PCPs). Patients at high-risk for non-completion of the flu vaccine will be randomized to an additional intensification nudge (compared with the multi-component nudge intervention alone).

All patients scheduled for a visit at the clinics randomized to the intervention arm will receive a pre-visit text message sent via Way to Health (a HIPAA compliant, approved platform) that informs the patient the flu vaccine has been reserved for them at their upcoming visit. Those patients that do not have a cell phone in the EHR will receive automated voice recording (AVR). For the patient intensification nudge, we will focus on patient subgroups within the clinic intervention arm that were identified through our previous analyses as high risk for not receiving a vaccine: age ≥ 70, Black race, residence in lower income communities (lowest quartile according to zip code), or no documented history of flu vaccine in the year prior. Patients who meet these criteria will be randomized 1:1 to receive an additional nudge via a bidirectional text messaging intervention versus no additional nudge. We will translate patient text messages for patients who require an interpreter according to their language preferences in the EHR. Translation will be available for Spanish and up to 4 additional languages based on site specific populations and technical capabilities. Our preliminary work identified the following five languages that account for 97.5% of the expected study sample: English, Spanish, Chinese, Vietnamese, and Russian.

For clinicians within the intervention arm, a flu vaccine order will be pended on their behalf prior to the PCP visit. This will frame vaccination as the default choice (opt-out rather than opt-in) while reducing clinician/care team effort by removing the need to individually order each vaccine. The unsigned order will be visible to the provider during the visit and they will maintain the option to sign or cancel the order.

In addition to the pended order, eligible clinicians within the intervention arm will receive a monthly peer-comparison feedback message describing their flu vaccine completion rate, relative to that of their peers. We will deliver this feedback via email and vary feedback based on clinicians' vaccine completion rates. PCPs whose completion rates are below the median rate will receive feedback relative to the median rate; PCPs whose completion rates are between the median and the 90th percentile will receive feedback relative to the 90th percentile, and those above the 90th percentile will not receive peer comparisons but will get positive feedback that they are high performers. This tiered approach has previously been shown to motivate clinician behavior and prevent regression to the mean among high performers. Figure 1 provides an overview of the study design. We will use this design to replicate our findings at a third site, Lancaster General Health.

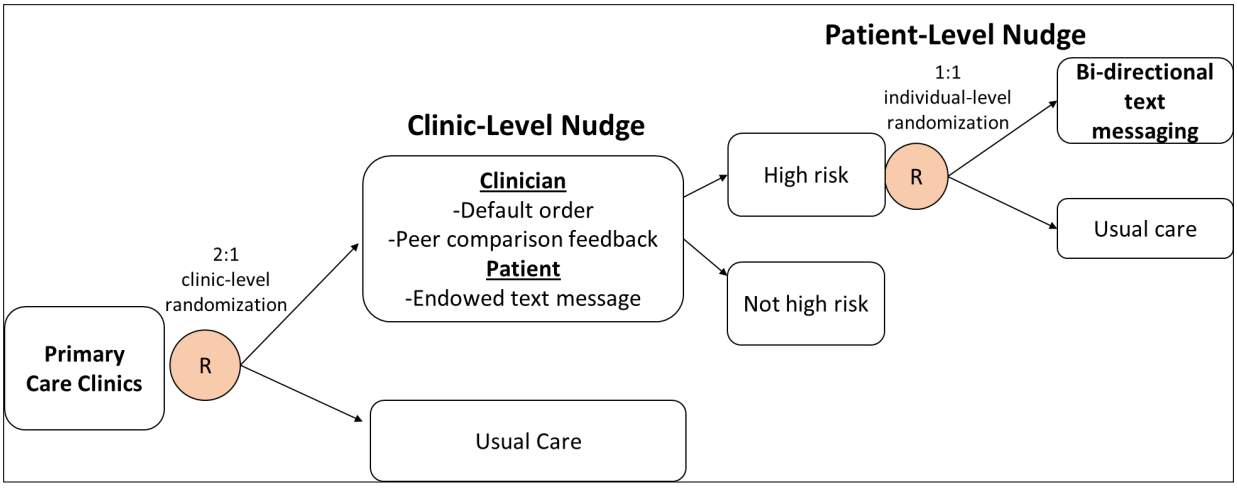

Figure 1. Overview of study design

5.2 Study sites

Penn Medicine and UW Medicine will be the primary sites for this trial, with Penn serving as the primary IRB site. Lancaster General Health is the study replication site.

5.3 Study duration

The study (including replication) is expected to take 3 years to complete including study preparation (year 1), trial intervention (year 2) and replication (year 3), analysis, and dissemination (year 3). The study intervention will run for 6 months during flu season (September – February).

5.4 Resources necessary for human research participation

The research staff spans the Penn Medicine Center for Health Care Innovation and Department of Medical Ethics and Health Policy to ensure Investigator support. This staff includes a study director, a project manager, research coordinator, and data analysts. To ensure that all staff assisting with research are adequately informed about the protocol and research related duties, the team will meet regularly both internally and with external stakeholders, including all research staff at partner sites University of Washington Medicine and Lancaster General Health, after which meeting minutes and task lists will be distributed. All members of the research team have completed CITI human subjects research training. Additionally, the protocol and related task sheets will be shared on a drive accessible to all staff members. The timeline has been constructed to allow for adequate time to conduct and complete the research. There are adequate facilities to ensure the research can proceed.

5.5 Target population

Patients ≥ 50 years of age in primary care clinics at Penn Medicine, UW Medicine, or Lancaster General Health, who have a scheduled new or return non-urgent/sick PCP visit at one of the study practices during the intervention period (September-February) and are eligible for the flu vaccination based on Health Maintenance data.

5.6 Subjects enrolled by Penn Researchers

Based off our power calculations and preliminary data work, Penn Medicine is expected to enroll approximately 51,152 patients.

5.7 Subjects enrolled by Collaborating Researchers

UW Medicine plans to enroll approximately 28,705 patients.

5.8 Accrual

Patients in this trial will accrue based on their eligible visit during the study period. An eligible visit is defined as the patient's first scheduled new or return non-urgent/sick visit in-person at an eligible clinical site during the study window. Patients in all study groups will be enrolled in the trial 4 days before their scheduled eligible visit.

5.9 Key inclusion criteria

Patient Inclusion Criteria

All patients must meet the following criteria to be eligible:

1) Age ≥50 years
2) A scheduled new or return (non-urgent/sick) primary care appointment at one of the study practices at the Penn Medicine, UW Medicine, or Lancaster General Health
3) Have not received their annual flu vaccine during the active intervention period (September- February)
4) Eligible to receive the flu vaccine

For the patient intensification nudge, at least one of the following criteria must be met to be considered high risk and randomized to receive the intensification nudge:

1) Age ≥ 70 years
2) Living in a lower income community (lowest quartile, zip-code based)
3) Did not receive a flu vaccine in the previous calendar year
4) Self-identifies as Non-Hispanic Black

Clinician Inclusion Criteria

Clinicians must meet the following criteria to be eligible to receive peer comparison feedback:

1) Practicing physician (MD, DO) or advanced practice provider (NP, PA) with the exception of residents and fellows
2) Have a minimum patient panel of at least 50 patients, and
3) Practicing at a clinical site randomized to receive the clinic-level nudge interventions.

5.9 Key exclusion criteria

Patients will be excluded from the study if they:

1) Have a documented allergy to flu vaccine
2) Have a flu vaccine exclusion modifier in Health Maintenance
3) Have opted out of research according to individual site guidelines and policies
4) Have no phone number (home or mobile) listed in their chart

6. Subject recruitment

Information on PCPs and their patients at Penn Medicine, UW Medicine, and Lancaster General Health will be obtained from the electronic health record using Clarity, an Epic reporting database.

7. Subject compensation

No compensation will be offered in this study.

8. Study procedures

8.1 Consent

A waiver of informed consent is requested and has been approved for this project in accordance with other, similar health system interventions and based on our prior meetings with the Penn IRB. This is a low-risk study conducted in partnership with clinical operations, and it is not feasible to consent every patient and clinician for a project of this scope, where the emphasis is on low cost, scalable interventions. Additionally, clinicians are being nudged towards evidence-based care that is standard of care within the three health systems for this project and based on the United States Preventive Services Task Force evidence-based guidelines. Patients and clinicians are not being forced into receiving a flu vaccine but, instead, this project is evaluating novel nudge interventions to help make it easier for clinicians and patients, especially those who are high risk, to deliver or receive evidence-based care. Patients and clinicians retain autonomy to not proceed with a vaccine for any given visit.

8.2 Procedures

--Interventions--

All patients in the intervention arm with a new or return, non-urgent/sick visit with a PCP will be identified 4 days before their scheduled appointment and sent an endowed text message 72 hours prior to their appointment (standard messaging). The message will inform the patient that a flu shot has been reserved for them at their upcoming appointment. A second nudge will be delivered at 24 hours prior to the scheduled appointment reminding them of their upcoming appointment and encouraging the patient to ask their PCP about receiving the flu vaccine.

In addition to the standard endowed text message nudge, high-risk patients randomized to receive the high-risk intensification nudge will also receive a bidirectional text intervention in the 72-hours prior to their visit. This intervention will query the patient about common questions or concerns about receiving the flu vaccine. If the patient responds, it will provide additional educational materials based on the patient's specific concern(s). If the intervention is unable to satisfactorily address a patient's questions or concerns, a final text will be sent 15 minutes prior to the eligible visit to remind the patient to discuss their unaddressed concerns with their PCP.

The first clinician nudge uses a default, pended order for the flu vaccine that will be visible to the provider during the visit encounter. Clinical staff will have the option of signing the order or dismissing it if they deem it inappropriate for a given patient.

The second clinician nudge is monthly peer comparison feedback that will be sent as an email facilitated by mail merge via Outlook or other bulk email platform per site preference. Clinicians will be told what percent of their eligible patients received the flu vaccine and how that compares to other peer clinicians in the intervention. If the completion rate is below the median rate, the clinician will receive feedback comparing their rate to the median. If it is above the median but below the 90th percentile, the clinician will receive feedback comparing their rate to the 90th percentile. If the clinician's rate is above the 90th percentile (defined as a top performer), they will receive an email informing them that they are a high performer. Residents and fellows will be excluded from the peer comparison analysis and messaging.

--Data--

Data on PCPs and their patients at Penn Medicine, UW Medicine, and Lancaster General Health will be obtained from Clarity (Epic's data reporting database). Clinician data includes gender and type of medical degree. Patient information includes demographic information, information about comorbid conditions (including diabetes, hypertension, and chronic kidney disease, and comorbid conditions needed to calculate the Charlson Comorbidity Index), contraindications for flu vaccine, appointment data, and flu vaccination administration.

--Randomization—

Primary care clinic level randomization will occur electronically. We will randomize clinics 2:1 to the nudge arm or control arm using covariate-constrained randomization.[10] Covariate-constrained randomization first enumerates a large number (e.g., 50,000) of possible intervention allocations. Then, a measure of covariate balance is computed with respect to a set of pre-specified covariates for each possible allocation. Finally, from a subset of possible allocations that achieve adequate covariate balance, one is randomly chosen as the final allocation of interventions for the study. We will implement a version of covariate-constrained randomization that stratifies by health system (Penn and UW) and balances the distribution of clinic size and panel risk across arms. The randomization procedure will be implemented in R[11] using the cvcrand package.[12] For the replication trial at Lancaster General Health, we will implement covariate-constrained randomization using the cvcrand package to balance the distribution of clinic size and panel risk across arms.

Within the high-risk patient subgroups, stratifying by intervention clinics, patients will be randomized 1:1 in Way to Health using permuted block randomization using random block sizes of 2, 4, and 6 to receive the additional intensification bidirectional text messaging nudge or standard messaging.

9. Analysis plan

Prior to analyses, we will produce data summaries to assess data quality, data distribution, and randomization success. To ensure even comparison across practices and arms, we will classify eligible patients at 4 days before a scheduled appointment for a new or return visit with their primary care clinician as being enrolled in the study. The primary analysis will be performed using an intention-to-treat approach. Specifically, patients who

do not show up to the first scheduled clinician visit will be considered enrolled and included in the primary analysis.

--Power Calculations--

For the following power calculations, we used an adjusted Type I error of 0.025 to account for two comparisons: 1) clinic-level nudges versus usual care, and 2) intensification for high-risk patients versus no intensification within practices where clinic-level nudges are provided. Based on retrospective data from our health systems, we will have 85% power to detect a 7-percentage point difference in the flu vaccine completion rate for comparison #1. This calculation assumed N=48 participating clinics across the two sites, an average cluster size of n=1385 patients, and an intracluster correlation (ICC) of 0.02. For comparison #2, we will have at least 99% power to detect a 2-percentage point difference even if the rate of vaccination in the high-risk group is 50%, the most conservative rate with respect to power. This calculation assumed 1:1 individual-level randomization of n=1000 high-risk patients within each of N=32 clinics that will be randomized to receive clinic-level nudges. These power calculations used combined retrospective data from Penn and UW to estimate the average number of patients per clinic and the number of high-risk patients who will be randomized. We expect to have greater power for both comparisons at the replication site which comprises more clinics and patients.

--Statistical Analysis--

The primary analysis will fit generalized estimating equations (GEE) with a binary outcome indicating whether a flu vaccine was received during the PCP visit (primary). Following the intention-to-treat framework, patients who do not complete their first scheduled visit will contribute a primary outcome of zero, indication a flu vaccine was not received during the PCP visit. We will also perform analyses based on a binary outcome that indicates whether a flu vaccine was received 3 months after the first scheduled visit, regardless of whether the visit was completed (secondary). An exchangeable working correlation will be specified at the clinic level for comparison #1 (evaluation of clinic-level nudges) and robust standard errors will be provided, clustered at the clinic level. An independence working correlation and robust standard errors without clustering will be used for comparison #2 (evaluation of individual-level nudges). In sensitivity analyses we will explore alternative specifications for the working correlation structure to examine robustness of parameter estimates and inference. In additional sensitivity analyses, we will censor patients with a PCP visit late in the intervention period (February/March) who are unlikely to complete a flu vaccine beyond March and will therefore not have a full 3 months to obtain a vaccine and examine completion rates among these patients.

We will examine effects of the interventions on overall rates of ordering. We will compare rates of ordering between the three intervention arms: 1) Control, 2) Clinic-level nudges only, and 3) Clinic-level nudges with intensification for high risk. We will fit a GEE with binary outcome indicating whether an order was signed or not. We will fit the model using the weighted and replicated approach[13] to account for the fact that low-risk patients seen in the clinics that received nudges are consistent with both intervention arms 2) and 3). We will include terms for the main effects of clinic-level and individual-level nudges as well as their interaction. We will test the appropriate linear combinations of the parameters that correspond to pairwise differences between each of the three intervention arms. An independence working correlation with robust standard errors will be

used to account for uncertainty in the weight distribution due to variability in the empirical proportion of high- versus low-risk patients.

We will account for the clinic-level covariate-constrained randomization by including health system, clinic size, and panel risk as covariates in the models for the effect of clinic-level nudges. In models for estimating the effect of intensification on high-risk patients, we will control for differences across health system by including clinic fixed effects which will also account for the stratified randomization.

We will perform exploratory subgroup analyses by risk group as it is defined for the individual randomization. For the low-risk strata, this will allow us to study the effect of the clinic-level nudges versus usual care amongst low-risk patients. For the high-risk strata, we will fit models that include each category used to define high risk (e.g., sex, race, previous year vaccination) as well as their interaction with treatment arm to determine which high-risk subgroups experienced the greatest benefits of the clinic- and individual-level nudges. We will also include a visit-level analysis with clustering by patient as an exploratory analysis.

Investigators and analysts will be blinded to study arm assignment during the intervention and analysis phases. The statistician is responsible for clinic-level randomization, but subsequently will be blinded to study arm assignment for the remainder of the intervention phase and analysis phase. Project staff (site PIs, project director, project manager, and study coordinators) will be unblinded during the intervention and analysis phases to complete daily study activities and prepare the blinded analysis files. Unblinding for investigators, statisticians, and analysts will be completed by the project staff and occur at the end of study analysis once all of the outcomes have been ascertained.

10. Investigators

Shivan Mehta, MD, MBA, MSHP is a Multiple Principal Investigator (MPI) and an Associate Professor of Medicine and Health Policy at the Perelman School of Medicine (PSOM). He has prior experience leading clinical trials to deploy interventions that leverage behavioral economics and technology to improve population health outcomes.

Amol Navathe, MD, PhD is a Multiple Principal Investigator (MPI), Associate Director of the Center for Health Incentives and Behavioral Economics, and Professor of Medicine and Health Policy at the Perelman School of Medicine (PSOM). He is a general internist and health economist with a research portfolio focusing on physician behavior. His expertise includes large-scale policy trial design in multiple health plans and health care organizations around physician incentives and high-value practice.

Joshua Liao, MD, MSc, FACP is a Multiple Principal Investigator (MPI) and Professor and Division Chief of the William T. and Gay F. Solomon Division of General Internal Medicine at University of Texas Southwestern Medical Center. He has prior experience designing and implementing nudge interventions in pragmatic randomized trials aimed at improving health care value and population health.

Kristin Linn, PhD is a Co-Investigator and an Assistant Professor of Biostatistics at the University of Pennsylvania. She has prior expertise in statistical methods for sequentially randomized clinical trials, predictive modeling, and machine learning techniques.

Kimberly Waddell, PhD, MSCI is a Co-Investigator and an Assistant Professor of Physical Medicine and Rehabilitation at the University of Pennsylvania and a Core Investigator at the Philadelphia VA Center for

Health Equity Research and Promotion . She has prior experience with clinical trials and nudge interventions to improve clinician and patient decision making.

11. Human research protection

11.1 Data confidentiality

Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information. Precautions are already in place to ensure the data are secure by using passwords and HIPAA-compliant encryption.

11.2 Subject confidentiality

Data on clinicians and patients will be obtained from Epic. Any information that is obtained will be used for research purposes only. Information on patients will only be disclosed within the study team and to the patient's PCP. All study staff will be reminded of the confidential nature of the data collected and contained in these databases.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). No source documents will be printed or maintained in paper form at the study sites. Operational data used for daily study management will be stored on a secure drive maintained behind the University of Pennsylvania Health System (UPHS) firewall. Analytic data will be stored within Penn Leonard David Institute's Health Services Research Data Center (HSRDC). HSRDC is maintained at a high-security level in accordance with federal regulations governing secure computer systems (e.g., the Federal Information Security Management Act-FISMA). The Way to Health (W2H) platform servers are based in the University of Pennsylvania Digital Academic Research Transformation (DART). The DART provides a secure computing environment for a large volume of highly sensitive data. DART requires all users of data or applications on DART servers to complete a DART-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. Curriculum includes HIPAA training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. W2H uses a role-based access control (RBAC) approach to assure that participant confidentially and study integrity is preserved. Access is granted by invitation only and can be revoked at any time. The W2H Team are employees of the University of Pennsylvania and Penn Medicine. All W2H team members have completed HIPAA Security training and CITI Protection of Human Subjects Research Training - ORA. Access to the backend database is restricted and only available to a select group of developers. The database is accessible only via a secure VPN (Virtual Private Network) and cannot be accessed from the public internet at all, i.e. authorized users can only access the databases from within Penn's network and over a secure VPN channel. Data from participating sites will be transferred to Penn (the data coordinating center) according to the methods defined in a fully executed Data Use Agreement. All data will be covered under the appropriate Data Use Agreements between Penn Medicine, UW Medicine, and Lancaster General Health and follow strict security guidelines.

11.3 Subject privacy

All efforts will be made by study staff to ensure subject privacy. Data will be evaluated in a de-identified manner whenever possible.

11.4 Data disclosure

Information on patients will only be disclosed within the study team and to the patient's primary care clinician (to whom this information is already available).

11.5 Protected Health Information/Data Protection

- Name
- Street address, city, county, precinct, zip code, and equivalent geocodes
- All elements of dates (except year) for dates directly related to an individual and all ages over 89
- Telephone and fax numbers
- Medical record numbers

11.6 Data and safety monitoring

A Data and Safety Monitoring Board (DSMB) is an independent group of experts convened to protect the safety of research subjects and to ensure that the scientific goals for the project are being met. While this study presents very low risk, the DSMB will be appointed by and act in an advisory capacity to the National Institute on Aging (NIA) to monitor participant safety, data quality and to evaluate the progress of the study. The Data and Safety Monitoring Plan (DSMP) will be reviewed and approved by the DSMB prior to study start. Detailed information about safety monitoring and reporting can be found in the Manual of Operating Procedures (Section 11) and the Data and Safety Monitoring Plan.

11.7 Risk/benefit

11.7.1 Potential study risks

There are minimal risks to PCPs and patients in this trial. Ordering an annual flu vaccine is a standard of care for these patients. The only research-related activity is the randomization of participants to different behavioral nudge strategies to increase flu vaccination uptake. Potential risks include patient frustration with messaging or outreach, duplicate flu vaccination within the recommended interval, or reaction requiring emergency department or hospital care among those with a previously known allergy or overdose of vaccine. Risks will be minimized by excluding any patients for which this study could be unsafe, i.e. if they have a documented allergy to the vaccine or documentation in their medical record that they have already received their flu vaccine this season.

There is a risk of breach of data and confidentiality. To minimize the risk of breach of data and confidentiality, we will use secure, encrypted servers to host the data and conduct the analysis. Operational data used for daily study management will be stored on a secure drive maintained behind the University of Pennsylvania Health System (UPHS) firewall. Analytic data will be stored within Penn Leonard David Institute's Health Services Research Data Center (HSRDC). HSRDC is maintained at a high-security level in accordance with federal

regulations governing secure computer systems (e.g., the Federal Information Security Management Act-FISMA). The Way to Health (W2H) platform servers are based in the University of Pennsylvania Digital Academic Research Transformation (DART). Data from participating sites will be transferred to Penn (the data coordinating center) according to the methods defined in a fully executed Data Use Agreement. All data will be covered under the appropriate Data Use Agreements between Penn Medicine, UW Medicine, and Lancaster General Health and follow strict security guidelines.

11.7.2 Potential study benefits

Receiving an annual flu vaccine is important for public health and the health of the patients. The EHR could be utilized to identify eligible patients, and patients at high risk for not receiving the vaccine and deliver nudges to help improve vaccine completion rates. The knowledge gained on how to increase flu vaccination rates could be applied to other populations and implemented at other health systems. PCPs may benefit from receiving feedback on their performance and having the vaccine order automatically ordered to help streamline the ordering process and prevent extra burden.

11.7.3 Risk/benefit assessment

The risk/benefit ratio is highly favorable given the potential benefit from eligible patients receiving a flu vaccine, especially those identified as high risk, that ordering and receiving a flu vaccine is within the standards of care in a primary care practice, and that efforts have been put into place to minimize the risk of breach of data.

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