CLINICAL TRIAL PROTOCOL

"Use of Construal Level Theory to inform messaging to increase vaccination against COVID-19"

National Clinical Trial (NCT) Identified Number: NCT04871776

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1. BACKGROUND AND SIGNIFICANCE

COVID-19 causes severe respiratory disease, disability, and death among older adults.[1] Vaccination is an essential step in the prevention of disease spread and mitigation of disease severity to promote healthy aging. Despite this, about 1 in 4 Americans report hesitation about receiving the COVID vaccine, even when free and reported as safe by scientists.[2] Moreover, hesitancy is higher among Black and Hispanic populations, which, if not directly addressed, could result in ongoing disparities in COVID infections and deaths.[3,4] Early efforts to vaccinate Americans has shown a lot of early demand, but racial disparities in vaccination rates are already emerging,[5] and once the initial interest from vaccine eager individuals has passed, interventions to engage more hesitant or resistant individuals will be needed to maximally protect the population from COVID-19.[6]

Patient outreach strategies for other vaccines have had modest success.[7–9] Most of these approaches have focused on abstract concepts of *why* patients should receive a vaccine. However, messages that describe *how* to do something may be more effective at inducing behaviors that are psychologically near (e.g., imminent, personal), like scheduling a vaccination appointment for yourself within a week.

According to Construal Level Theory, emphasizing "why" elicits more abstract thinking, or high-level construals, and can induce an emotional mindset, which could challenge an individual's sense of identity, autonomy, or political preferences. Conversely, emphasizing "how" is more cognitive and evokes concrete thinking, or low-level construals, and encourages a planning or implementation mindset.[10,11] Low-level construals ("how" messages) have been shown to increase intention to or uptake of several heath behaviors including dietary changes,[12] use of relaxation techniques,[13] blood donation,[14] and completion of biometric screening and health surveys.[15] Though prior studies of vaccine acceptance have not explicitly applied Construal Level Theory, aspects of interventions that elicit low-level construals have been successful compared to other techniques. For example, straightforward messages stating that a dose of the flu vaccine was "reserved" for the patient at their upcoming appointment (low-level construal) were more effective than messages about protecting loved ones (high-level construals).[16] Similarly, information on where and when to receive the flu shot outperformed gain- or loss-framed reminder messages,[8] and a map of flu vaccine locations was more effective than a loss-framed message or an entry to win a $100 gift card.[17]

Because of the political and emotional valence of the COVID-19 vaccine, "how" messaging to elicit concrete thinking may be particularly important. Direct comparison of "how" vs "why" messages has not been tested for vaccines, and it has never been tested for COVID-19. Moreover, COVID vaccine hesitancy differs by age, gender, and race,[4,6] and demographic groups may respond differently to messages. Tailoring a message to a specific group with higher rates of vaccine hesitancy could help reduce health disparities.

Thus, in this study we propose a pilot randomized trial to test the effects of "how" vs "why" framing on COVID-19 booster vaccination rates using electronically delivered communication (e.g., patient portal messages delivered through the electronic health record [EHR]), followed by analyses to identify patient characteristics that might predict intervention responsiveness to allow for further tailored communication after the completion of the trial.

2. SPECIFIC AIMS

The main aims are to 1) test the effect of "how" vs "why" framed messages on the rates of COVID-19 booster vaccination and 2) assess association of clinical and demographic characteristics with intervention responsiveness.

The objectives and endpoints for this project are summarized below.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1		
To test the effect of "how" vs "why" framed messages on the rates of COVID-19 vaccination	*Primary:* the rate of booster vaccination at the targeted visit *Secondary:* the rate of receipt of a COVID booster vaccine within 6 weeks of the targeted visit	These outcomes are directly related to the interventions, are clinically meaningful, and are measurable using routinely collected data in the Mass General Brigham COVID-19 Vaccine Registry and the Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW). We plan to use RPDR for variable collection as long as all the variables needed are available in the RPDR. If a variable is not available in the RPDR then we will supplement with use of the EDW for those variables.
Aim 2		
To assess association of clinical and demographic characteristics with intervention responsiveness	A model to predict likelihood of response to each intervention based on patient characteristics	A model predicting intervention responsiveness could be used to tailor future interventions to specific patients

3. SUBJECT SELECTION

This study will include patient subjects for intervention and analysis. We will use the Mass General Brigham Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW) to identify Mass General Brigham (MGB) patients age ≥18 who are eligible for the COVID booster vaccine, who have not received a dose as of the time of upcoming primary care clinic visit. We will then cross check that with the COVID-19 vaccine registry so that we can additionally exclude patients who may have received a vaccination that has not yet been entered into RPDR.

Patients will be excluded if they did not receive the full set of their primary COVID-19 series or had a severe allergic reaction to either dose of their primary series. All MGB patients who meet the criteria above will be eligible for the study. We plan to begin the study after the booster vaccine is widely available to individuals 18 years of age or older. Based on a recent survey data from the Kaiser Family Foundation, at least 45% of the fully-vaccinated population are at least somewhat skeptical about obtaining a booster vaccination.

4. SUBJECT ENROLLMENT

4.1 Methods of enrollment

We will use the Mass General Brigham COVID-19 Vaccine Registry and Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW) to identify eligible patients. The COVID-19 Vaccine Registry contains identified patient data, including the type of vaccine administered, first or second dose, as well as when and where the patient received their vaccine. The registry integrates information from vaccines administered by MGB, administrations entered into Epic based on patient report, and the state's Massachusetts Immunization Information System (MIIS) that includes vaccination sites across the state. General patient demographic information, adverse reactions and patient identifiers are included in the COVID-19 Vaccine Registry.

We will thus use the Mass General Brigham COVID-19 Vaccine Registry and EHR information in the Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW) to identify MGB patients age ≥18 with an upcoming primary care outpatient appointment who are also eligible for the COVID booster vaccine based on routinely-collected data from these sources. We plan to launch the study after the booster vaccine has become widely available to adults and supply of vaccines at MGB is anticipated to be sufficient. Because the intervention cost is extremely low per patient, we plan to include all eligible patients.

4.2 Informed consent

As with other minimal-risk studies we have performed where informed consent is impracticable, we are requesting a waiver of informed consent and HIPAA authorization. There are several reasons for this. One, the nature of this communication-oriented intervention involves testing different messaging types utilizing secure communication channels that are already in use in routine clinical care. Second, the ability to understand the true effect of the intervention as it is delivered in the real world would be impossible to ascertain if formal informed consent from patients were sought. Third, obtaining formal informed consent would likely reduce the number of patients participating in the study, especially those from under-represented populations, and therefore undermine the generalizability of the study results, a foundational aspect of pragmatic clinical trial principles. Fourth, it would be extremely impractical as we expect more than 5,000 patients to still be eligible at the time of study launch. Fifth, contacting them in advance would actually introduce a co-intervention and reduce the ability to interpret the study findings. Finally, we will launch this project with approval by appropriate clinical leadership.

4.3 Treatment assignment and randomization

All eligible patients will be randomized to one of three arms: 1) "why" messaging, 2) "how" messaging, or 3) "standard of care ("usual care"). We plan to conduct stratified randomization based on the primary care clinic the patient attends to account for differences in patient populations between clinics. We will also use block-stratified randomization, in which the unit of randomization is the day of the week the study visit is on. This choice was made in response to the logistical difficulties randomizing at the patient level presented. Each weekday, eligible patients will be identified that have an upcoming visit 2-3 days from then. The day of the week of that visit will be randomized in a 1:1:1 ratio with a random number generator to one of three arms: 1) "why" messaging, 2) "how" messaging or 3) "standard of care" ("usual care").

5. STUDY PROCEDURES

5.1 Study Site

Study participants will be selected from Mass General Brigham (MGB), a large integrated delivery network in Boston, MA, specifically from Mass General Hospital primary care clinics, where Dr. Haff practices.

5.2 Overall Design

We will use the Mass General Brigham COVID-19 Vaccine Registry and EHR information in the Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW) to identify all patients age ≥18 with an upcoming primary care outpatient appointment who are eligible for the COVID booster vaccine. We plan to launch the study after the booster vaccine has become widely available to adults over age 18 and supply of vaccines at MGB is anticipated to be sufficient. All eligible patients will be randomized to one of three arms: 1) "why" messaging, 2) "how" messaging, or 3) standard of care ("usual care"). We will conduct stratified randomization based on the primary care clinic the patient attends and day of the week the upcoming visit is on.

The primary outcome will be the rate of booster vaccination at the targeted visit. Secondary outcome will be receipt of a booster vaccine within 6 weeks of the target visit at any location. After completion of the trial, we will utilize data from the RPDR and/or EDW to develop models that predict which patients are most likely to respond to each intervention using patient baseline characteristics, which in the future could allow for targeting of interventions to specific patients. We will use the Mass General Brigham COVID-19 Vaccine Registry and the RPDR/EDW for outcome measurement.

5.2.1 Aim 1 Design

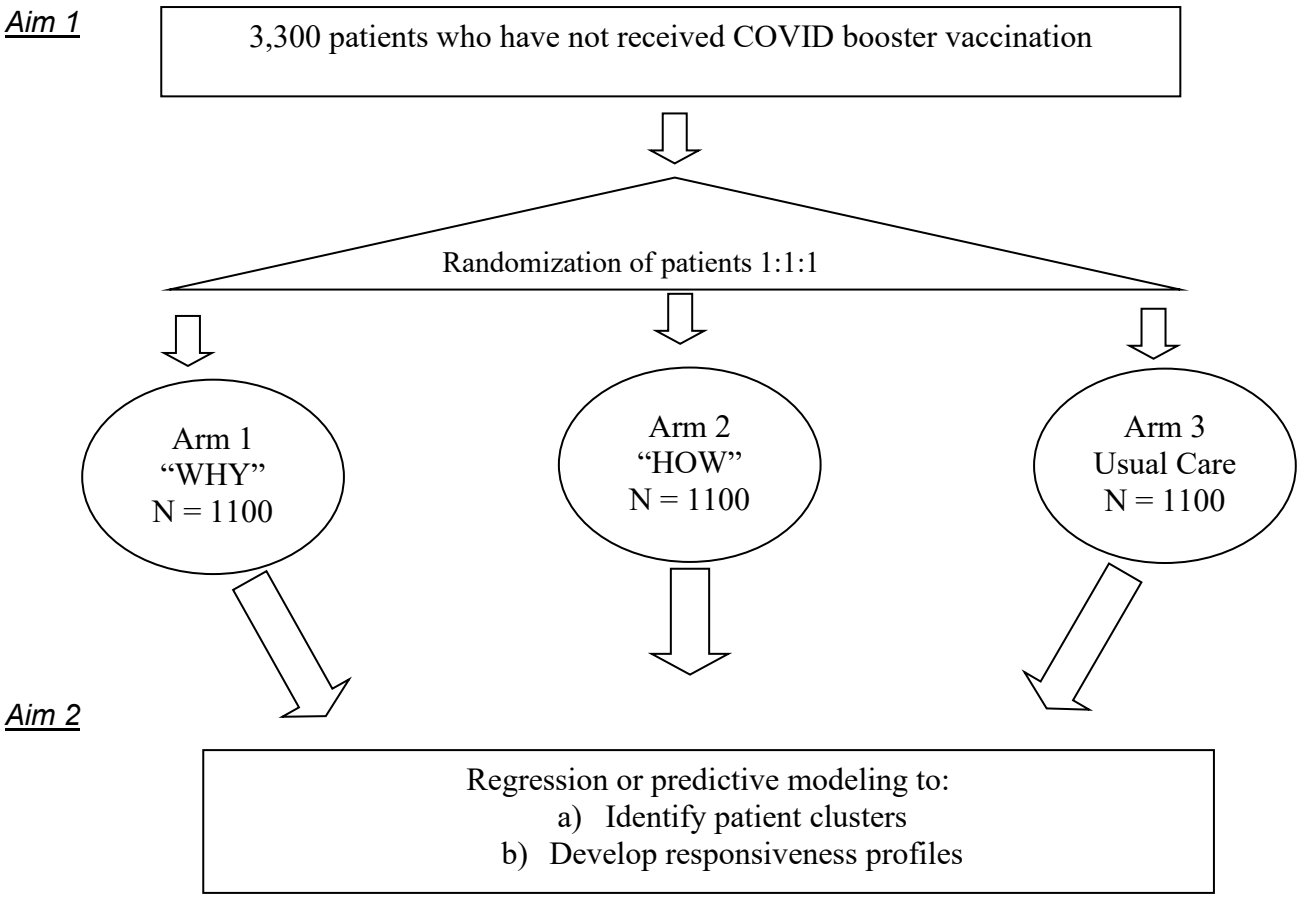
In Aim 1 of the study, we will conduct a 3-arm randomized controlled trial to compare the effectiveness of two interventions compared to usual care on COVID-19 vaccination uptake. We will include Mass General Brigham (MGB) patients age ≥18 with an upcoming primary care outpatient visit with a Mass General Hospital primary care provider who are eligible for the COVID booster vaccine and who have not received a dose. This approach has been approved by MGH primary care leadership. Patients will be excluded if they did not receive the full set of their primary COVID-19 series.

Patients will be randomized equally to one of three arms: 1) "why" messaging, 2) "how" messaging, or 3) standard of care ("usual care"). We plan to conduct stratified randomization based on the primary care clinic the patient attends to account for differences in patient populations between clinics and based on the day of the week the upcoming visit is on to minimize logistic difficulties in the intervention delivery. "Why" messages will focus on reasons to get the vaccine, including protecting self and loved ones or the idea of herd immunity. "How" messages will focus on the details of obtaining a vaccination at MGB, what to expect, and how to prepare for the visit. The messages will be sent through the EHR electronic patient portal for portal users. For patients whose primary language listed in the EHR is not English, they will be offered translated messages following standard MGB Gateway messaging practices. Gateway messages will first include a message translated in their primary language (Spanish, Portuguese, Arabic, Chinese, Russian, Haitian Creole or Bosnian) followed by an English version of the message. Consistent with recent studies for influenza vaccination and the approach approved by MGH primary care leadership, we will send a message to patients a few days in advance of their office visit.[16] Based on current MGH practice (i.e., standard of care), patients in Arm 3 will not receive any additional message about their upcoming visit, beyond what they already receive by MGH. **Initial examples of these messages are attached**.

5.2.2 Aim 2 Design

In Aim 2, we will assess association of clinical and demographic characteristics with intervention responsiveness. To do this, we will measure baseline patient clinical, historical, and demographic characteristics. Characteristics measured from the RPDR/EDW will include age, gender, race, prior influenza vaccine history, and comorbidities that increase risk of severe COVID disease, among others. We will also measure zip-code linked variables including mean household income, education level, rurality, and prevalence of COVID in the patient's surrounding community. We will develop models that predict which patients are most likely to respond to each intervention using patient baseline characteristics, which in the future could allow for targeting of interventions to specific patients.

5.3 Study Schema



5.4 Scientific rationale for study design

The use of a randomized trial design will be able to both provide stronger evidence of causality in the effectiveness of the interventions and allow for empiric derivation of patient characteristics that may influence intervention responsiveness. An observational study design or patient self-report of factors that influence intervention responsiveness are more subject to bias.

5.5 Justification for intervention

According to Construal Level Theory, emphasizing "why" elicits more abstract thinking, or high-level construals, and can induce an emotional mindset, which could challenge an individual's sense of identity, autonomy, or political preferences. Conversely, emphasizing "how" is more cognitive and evokes concrete thinking, or low-level construals, and encourages a planning or implementation mindset.[10,11] Low-level construals ("how" messages) have been shown to increase intention to or uptake of several heath behaviors including dietary changes,[12] use of relaxation techniques,[13] blood donation,[14] and completion of biometric screening and health surveys.[15] Though prior studies of vaccine acceptance have not explicitly applied Construal Level Theory, aspects of interventions that elicit low-level construals have been successful compared to other techniques.

Because of the political and emotional valence of the COVID-19 vaccine, "how" messaging to elicit concrete thinking may be particularly important Direct comparison of "how" vs "why" messages has not been tested for vaccines, and it has never been tested for COVID-19. Moreover, COVID vaccine hesitancy differs by age, gender, and race,[4,6] and demographic groups may respond differently to messages. Tailoring a message to a specific group with higher rates of vaccine hesitancy could help reduce health disparities.

5.6 End-of-study definition

The active interventions in Aim 1 are expected to last no more than 1 week. The study data collection of vaccination receipt will begin after the target primary care outpatient visit will conclude 1 month after the target visit is complete, as we anticipate some lag for complete vaccination information to be included in the MGB COVID-19 Vaccine Registry data source. Development of the prediction models will be done following Aim 1 data collection.

5.7 Data sources

Sources of research material, data that will be recorded, when data will be collected

Data regarding patients' medical history, disease control, medication use and health care utilization will be obtained from The Mass General Brigham COVID-19 Vaccine Registry and EHR data from the Research Patient Data Registry (RPDR) and/or Enterprise Data Warehouse (EDW), supported by Epic Systems, Inc.

The Mass General Brigham COVID-19 Vaccine Registry is a secure repository of data containing COVID-19 vaccine administration, utilization and adverse event information for analysis by the research community. This registry contains identified patient vaccination data for patients with a record of any type or dose of the COVID-19 vaccine. The data lives on a secure server within the Mass General Brigham firewall. It is only accessible to IRB-approved researchers. The data in the registry is updated every week. Its usage is logged and audited.

The Enterprise Data Warehouse for Epic EHR data resides in an Oracle 9i environment and consists of the Clarity and Payer databases. The Clarity database is a relational database that contains clinical and financial information from the Epic Suite of products; including the electronic medical record system (EpicCare), the appointment scheduling system (Cadence), the patient accounting system (Resolute), the patient web portal and the master patient index (Identity). The various tables within the Clarity database are refreshed on a daily, weekly or monthly basis. The data extracts obtained from the RPDR/EDW are maintained on secure MGB servers housed at the Division of Pharmacoepidemiology in the Department of Medicine at BWH.

Linkages to subjects, access to subject identities

Individually identifiable data are required to link patients between the Mass General Brigham COVID-19 registry and the RPDR/EDW, and to send messages to patients as part of this trial. Without this linkage, we could not fulfill the study's objectives. To protect the confidentiality of these data, only the minimal necessary research staff will have access to personal identifiers. After the intervention is completed and study variables are created, all identifiable information will be deleted from the study database. All research staff are properly trained in research management and will be approved by the IRB. All personally identifiable health information will be kept under lock and key.

Schedule of activities

	Screening	Enrollment	Intervention	Analysis
Identification of eligible patients	X			
Randomization		X		
Control and experimental interventions			X	
Primary outcome analysis				X
Predictive modeling analysis				X

6 BIOSTATISTICAL ANALYSIS

6.3 Statistical Hypothesis

The null hypothesis is that rates of COVID booster vaccination will be equal in both of the intervention groups when compared to control.

6.4 Samples size determination

Sample size estimates suggest that ~1,100 individuals in each arm will allow us to observe a 5% difference in vaccination rates compared to the usual care arm, assuming a usual care arm vaccination rate of 20% as well as assumptions of alpha=0.05 and power=0.80. Given that more than 1 million patients receive care at MGB, we expect to identify at least 5,000 patients who have not yet received the booster vaccination at the outset of the trial and who will be eligible to receive one of the messages. This will also provide sufficient power for secondary outcomes. Under the same assumptions, we should be able to observe a <6% difference in 6-week vaccination rates compared to usual care, assuming a usual care arm vaccination rate of 25%.

6.5 Statistical analyses

6.5.1 Analysis of the primary endpoint

The primary outcome will be the rate of receipt of COVID booster vaccine dose in each arm at the target primary care outpatient appointment, treated as a binary outcome. We will use logistic regression to compare outcomes between each intervention arm versus usual care and against each other. Of note, we chose not to formally adjust for multiple testing in the primary analysis for several reasons. First, although the chance of finding at least one false positive among several tests is >5%, a Bonferroni correction would be much too conservative in this case, because the multiple comparisons among the treatment arms share the same four exposure groups. Second, a recent systematic review of multiple arm trials showed that more than half of all randomized trials with multiple exposure groups do not adjust for multiple comparisons,[18] reasoning that if each exposure was compared with control in a separate trial, no adjustment would be necessary.

6.5.2 Analysis of the secondary endpoints

Secondary outcomes will include in each arm the rate of receipt of COVID booster vaccine 6 weeks after the target primary care outpatient appointment. . As in the primary analysis, we will use the MGB Research Patient Data Registry (RPDR) and/or Electronic Data Warehouse (EDW) for outcome measurement. We will use logistic regression to compare outcomes between each intervention arm versus usual care and against each other; in secondary analyses, we will additionally adjust for any imbalanced baseline characteristics.

6.5.3 Baseline descriptive analyses

We will report the means and frequencies of baseline variables for eligible patients.

6.5.4 Exploratory analyses

In subsequent analyses, we will develop a model to predict intervention responsiveness based on observable patient characteristics. We will fit separate logistic and boosted regression models using sets of these predictors to evaluate the ability to predict responsiveness to each messaging type. Boosted regression is a machine learning method robust to multi-collinearity and overfitting.[19,20] For each, we will use 10-fold cross-validation to compare C-statistics for the ability to predict intervention response and calculate a continuous net reclassification index to assess changes in predicted response with additional predictors.[21,22] We will also measure the relative influence of predictors to determine those that are most influential at predicting intervention responsiveness for a given arm.

7 RISKS AND DISCOMFORTS

We believe there is no more than minimal risk involved to patient subjects, as subjects will be receiving COVID-19 booster vaccination information through routine communication methods that will encourage the uptake of a vaccine recommended by the CDC and MGB in order to prevent COVID-19 disease. The study team will not be providing any direct care to patients and all vaccination decisions will ultimately be made by the patient, with the potential consultation of their medical team at Mass General Brigham. Thus, the main potential risk to subjects in this study is related to privacy of data, and we will take several measures to ensure that this risk is minimal, and that patient information is safeguarded.

Patient data for study outcome evaluation will be drawn from the Mass General Brigham COVID-19 Vaccine Registry and EHR information in the Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW). The Mass General Brigham COVID-19 Vaccine Registry is a secure repository of data containing COVID-19 vaccine administration, utilization and adverse event information for analysis by the research community. The investigators are aware of the sensitive nature of the data and are committed to protecting patient privacy. Only the minimum necessary identifiable health care data needed to achieve the intended purpose will be used. All the data in the registry is contained within the Mass General Brigham firewall, and its usage is logged and audited. It is only accessible to IRB-approved researchers.

For all study data, we will safeguard any identifiable information in accordance with IRB practices, limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training, and store any data in accordance with IRB practices. Finally, as is our routine practice, great care will be taken to ensure the confidentiality of all data and to protect the privacy of participants through translation of all potentially traceable identifiers into untraceable coded subject numbers whenever possible.

Of note, MGB has already set up an internal safety reporting system, which records any adverse events occurring after receipt of the vaccine and escalates serious medical issues resulting from vaccination to the patient's provider as appropriate. Additionally, the CDC has also set up mechanisms to track vaccine safety. As such, any effort to collect information on vaccine side effects for our subjects would be duplicative and we will therefore not capture safety events through our own independent tracking system. However, we will be in regular contact with MGB clinical leadership and will be notified if patients or staff reach out to MGB with feedback about the intervention messages.

8 POTENTIAL BENEFITS

The potential benefits to study participants include protection against COVID-19 disease if they choose to get vaccinated. Additionally, society may benefit in the future from potentially higher vaccination rates and the accumulated knowledge that originates from this research.

9 MONITORING AND QUALITY ASSURANCE

9.3 Ethical conduct

General oversight of the project by the principal investigators (Drs. Haff and Lauffenburger) will occur throughout the study period, including regular contact with clinical leadership to obtain ongoing feedback. In addition, this protocol will undergo Institutional Review Board (IRB) evaluation by an institutional IRB. Study data will be accessible at all times for the principal investigators and co-investigators to review, if applicable. The principal investigator will review study conduct (e.g., protocol deviations) on a monthly basis. The principal investigators will also ensure that all protocol deviations for the trials are reported to the NIH and the IRB according to the applicable regulatory requirements. We are also using an NIA-appointed Safety Officer (SO) for this study.

The study team will not be providing any direct care to patients, and all vaccination decisions will ultimately be made by the patient, with the potential consultation of their medical team at Mass General Brigham. Any adverse events will be handled in the course of regular clinical care. Given the minimal risks involved in participation in this study, we do not anticipate any unacceptable adverse events. However, our plan for data and safety monitoring does include multiple mechanisms to ensure minimal risk of participation in the research.

Of note, **MGB has already set up an internal safety reporting system, which records any adverse events occurring after receipt of the vaccine and escalates serious medical issues resulting from vaccination to the patient's provider as appropriate**. Additionally, the CDC has also set up mechanisms to track vaccine safety. As such, any effort to collect information on vaccine side effects for our subjects would be duplicative and we will therefore not capture safety events through our own independent tracking system. However, we will be in regular contact with MGB clinical leadership and will be notified if patients or staff reach out to MGB with feedback about the intervention messages.

However, if we receive communication from MGB leadership or participants themselves and thus we become aware of any AEs or SAEs throughout the course of the study, we will collect this information. Any reports of deaths will be submitted to the NIA Program Officer and to the SO within 24 hours. Any unexpected SAEs will be reported to the NIA PO, SO and the IRB within 48 hours of the study's knowledge of the SAE. All other reported SAEs and AEs received by the study team will be reported to the NIA Program Officer and to the SO quarterly.

9.4 Informed Consent

As with other minimal-risk studies that utilize routinely collected patient data, **we request a waiver of informed consent and HIPPA authorization.** There are several reasons for this. One, the nature of this communication-oriented intervention involves testing different messaging types utilizing secure communication channels that are already in use in routine clinical care and will be done in collaboration with MGB leadership. Second, the ability to understand the true effect of the intervention as it is delivered in the real world would be impossible to ascertain if formal informed consent from patients were sought. Third, obtaining formal informed consent would likely reduce the number of patients participating in the study, especially those from under-represented populations, and therefore undermine the generalizability of the study results, a foundational aspect of pragmatic clinical trial principles. Finally, we expect

approximately 5,000 individuals to be eligible at the time of the messaging, and contacting them in advance would introduce a co-intervention as well as be impracticable.

9.5 Confidentiality and privacy

Data will be extracted from the Mass General Brigham COVID-19 Vaccine Registry and EHR information in the Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW) at MGB. The COVID-19 Vaccine Registry contains identified patient data, including the type of vaccine administered, first or second dose, as well as when and where the patient received their vaccine. General patient demographic information, adverse reactions and patient identifiers are included in the COVID-19 Vaccine Registry. The investigators are aware of the sensitive nature of the data and are committed to protecting patient privacy. Only the minimum necessary identifiable health care data needed to achieve the intended purpose will be used. All the data in the registry is contained within the Mass General Brigham firewall, and its usage is logged and audited. The data extracts obtained from the RPDR/EDW are similarly maintained on secure MGB servers. RPDR/EDW extracts are continuously used by clinical operations staff for quality assessment and improvement, and undergo routine, rigorous peer-review by experienced data analysts to ensure accuracy and completeness. Patient identifiers will be needed to link RPDR/EDW data to COVID vaccine registry data and to send messages to patients. Once all data linkages and study interventions have been completed, patient identifiers will be removed and replaced with study IDs for data analysis.

Data for the study will be safeguarded by state-of-the-art security protocols. The facilities have 24-hour security and are protected by locked entrances. MGB has computer networks in place that employ up to date virus protection software and enable password protected access only to study investigators. The setup for analysis of these data will be the same as all the other IRB applications that our MGB research division submits for secondary use of data. All the datasets, including limited protected health information (PHI), will be stored only on secure servers at MGB's data center and will only be accessed by a limited number of individuals in the study team from this division who are all trained in data security and patient privacy.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB's data center. The MGB data center is a secure facility that houses both computing environments as well as clinical systems and electronic medical records for several large hospitals in Eastern Massachusetts. Entry into the computer room requires staffed computer room security. The Division of Pharmacoepidemiology's computers are connected to the MGB networking backbone with 10 gigabit-per-second fiber links. Network security is overseen by electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current Department of Defense standard for data security, and are stored in a locked facility. The redundancy, extensive data power, and security of our computer facility confirm our capacity to collect and manage data and ensure confidentiality for all project participants.

We will also safeguard any identifiable information from the physicians in accordance with IRB practices, limit access to any information in accordance with IRB practices, limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training.

All members of the research team have completed or will complete appropriate human subjects research training and patient privacy training related to the Health Insurance Portability and Accountability Act (HIPAA).

9.6 Safety oversight

We believe this study involves no more than minimal risks to subjects, and we do not anticipate any additional adverse events above what is experienced in routine COVID-19 vaccination practice. General oversight of this project by the Brigham and Women's Hospital (BWH) co-leads (Drs. Haff and Lauffenburger) will occur throughout the study period, including regular contact with MGB clinical leadership involved in the project to obtain ongoing feedback.

As described above, this study will include safety monitoring from an NIA-appointed independent safety officer (SO) to perform data and safety monitoring activities. This SO will advise NIA Program staff and the PIs regarding participant safety, study risks and benefits, scientific integrity, participant recruitment, and ethical conduct of the study. The SO will act in an advisory capacity to the NIA PO and to evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome. The SO will make recommendations to the NIA PO concerning the continuation, modification, or conclusion of the trial.

The study team will prepare safety reports at least biannually to be reviewed by the SO and NIA for recommendations for or against the trial's continuation, as well as any modification to the study. In addition to safety data, the SO will consider recruitment and retention rates and whether delayed recruitment raises concerns of futility or ethical considerations.

9.7 Benefit risk assessment

9.7.1 Known potential risks

We believe there is no more than minimal risk involved to the patient subjects, as subjects will be receiving COVID-19 vaccination information through routine communication methods that will encourage the uptake of a vaccine recommended by the CDC and MGB in order to prevent COVID-19 disease. The study team will not be providing any direct care to patients and all vaccination decisions will ultimately be made by the patient, with the potential consultation of their medical team at Mass General Brigham. Thus, the main potential risk to subjects in this study is related to privacy of data, and we will take several measures to ensure that this risk is minimal and that patient information is safeguarded.

9.7.2 Known potential benefits

Use of Construal Level Theory for optimizing vaccination information could help increase COVID-19 booster vaccine uptake by MGB patients. Thus, the potential benefits to study participants include protection against COVID-19 disease if they choose to get vaccinated. Additionally, society may benefit in the future from potentially higher vaccination rates and the accumulated knowledge that originates from this research.

9.7.3 Assessment of potential risks and benefits

We will enroll patient-subjects based on their being eligible for the COVID-19 vaccine identified through the Mass General Brigham COVID-19 Vaccine Registry and Research Patient Data Registry (RPDR) and/or Epic Enterprise Data Warehouse (EDW). We also request a HIPAA waiver of patient authorization to access the HER data necessary for outcome evaluation. The main potential risk to subjects in this study is related to privacy of data, and we will take measures to ensure minimum necessary use of identifiers and that all data are safeguarded. Individually-identifiable data are required to link patients between the Mass General Brigham COVID-19 registry and the RPDR/EDW, and to send messages to patients as part of this trial, and without this linkage, we could not fulfill the study's objectives. To protect the confidentiality of these data, only the minimal necessary research staff will have access to personal

identifiers. All personally identifiable health information will be kept under lock and key. After the intervention is completed and study variables are created, all identifiable information will be deleted from the study database. Data for the study will be safeguarded by state-of-the-art security protocols and handled in accordance with IRB policies. All research staff are properly trained in research management and will be approved by the IRB.

10. LIST OF REFERENCES

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