Supplement

Behavioral Science and Hepatitis C Outreach Among Primary Care Patients

This supplement provides additional information about the work. It contains the following items:

Initial Protocol

Behavioral Science and Hepatitis C Screening Outreach Among Primary Care Patients

Brief Description

This project aims to evaluate different approaches to increase Hepatitis C screening among primary care patients at Penn Medicine through a centralized screening outreach program. In a pragmatic trial, we will evaluate different approaches to increase completion of screening among eligible patients, including changing the default from opt-in to opt-out and incorporating behavioral science principles into the outreach communication.

Protocol

Abstract

Hepatitis C is treatable with effective medications, but only about half of primary care patients in the appropriate age group are up-to-date on screening. In this project, we will evaluate different ways to reach out to eligible patients to encourage them to participate in screening. Through letters and the electronic health record portal, we will compare an opt-out approach and language incorporating behavioral science principles to traditional outreach messaging with the goal of increasing Hepatitis C screening uptake.

Objectives

Overall objectives

We will develop and evaluate a centralized approach to increasing Hepatitis C screening rates through direct outreach to patients' homes. This pragmatic randomized controlled trial has the following aims: Aim 1: To compare opt-out screening outreach with a signed order to traditional opt-in screening outreach. Aim 2: Among active electronic health record portal users, to compare electronic and mailed outreach. Aim 3: To compare messaging that incorporates behavioral science principles to standard messaging about HCV screening.

Primary outcome variable(s)

The primary outcome will be the percentage of patients who complete HCV antibody testing within 4 months of initial outreach.

Secondary outcome variable(s)

Secondary outcome will be completion of HCV antibody testing within 12 months of initial outreach. We will also look at the percentage of tests that are positive, those with detectable viral loads, and the percentage that are referred to and receive HCV treatment and cure.

Background

The hepatitis C virus (HCV) is the leading cause of liver transplant and hepatocellular carcinoma in the US. New direct-acting antivirals are available that can eradicate the disease in over 95% of those that are treated, with minimal side effects. As a result of new therapies and a five-fold higher risk among baby boomers, the US Preventive Services Task Force and CDC now recommend HCV screening for all

patients born between 1945 and 1965. Of the estimated 3.2 million people chronically infected with HCV, about 75% were born during this time frame. Despite this, national rates of screening among this group remain low at less than 30%. If more people could get screened, we could potentially identify more undiagnosed disease and help navigate to treatment. At Penn Medicine primary care practices, HCV screening rates have risen from 37% in 2014 to 61% in 2017, likely from a combination of provider educational efforts and EHR alerts. There is also significant practice variation ranging from 4% to 99% screening rates. While EHR alerts have been shown to increase HCV screening rates, there is potential to complement this with direct outreach to patients homes, as has been incorporated into cancer screening initiatives. Additionally, there is a mandate from the state of Pennsylvania requiring health care providers to offer HCV testing to all primary care patients. There is an opportunity to provide direct outreach to all eligible primary care patients at Penn Medicine, while also evaluating different approaches to increasing HCV screening rates. Insights from behavioral science have been shown to increase participation in health promoting behaviors in a variety of ways. Switching from opt-in to opt-out framing has been shown to triple patient participation in remote monitoring and CRC screening. Additionally, messaging that incorporates social norms, reciprocity, and precommitment have also been shown to increase participation. However, it is not clear how these approaches would translate to HCV screening.

Study Design

Design

This is a pragmatic randomized controlled trial with two parts. Pilot A is a cluster randomized controlled trial with 1:1 randomization at the provider level to an opt-in or opt-out approach. Pilot B is a patient-level randomized controlled trial with factorial design. Active EHR portal patients will be randomized in a 1:5 ratio to letter or EHR messages. Additionally, all patients in part B will be randomized in a 1:1 ratio to usual care messaging or behavioral science messaging.

Study duration

We anticipate 2 months to recruit providers, identify eligible patients through electronic data extraction, and conduct initial outreach. We will then follow patients for 12 months after initial outreach. We plan to start enrollment in September 2018.

Resources necessary for human research protection

Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.

Dr. Shivan Mehta is the PI of this study. He is a gastroenterologist and assistant professor of medicine at the Perelman School of Medicine, University of Pennsylvania. All members of the research team have completed CITI human subjects research training. Standard Operating Procedure documents for the project will be accessible to all members of the research team, which will keep research staff informed about the protocol and their related duties. There are adequate facilities to conduct the research; all research staff have adequate office space on the UPenn campus.

Characteristics of the Study Population

Target population

Primary care patients at Penn Medicine born between 1945-1965 and not up-to-date with screening for Hepatitis C.

Subjects enrolled by Penn Researchers

30022

Subjects enrolled by Collaborating Researchers

0

Subject Recruitment
30,022 patients will be identified through automated data extraction from the electronic health record (EHR). All eligible patients in primary care will receive outreach through the study.

Accrual

We will conduct the study in close partnership with the Primary Care Service Line, who has agreed to include all patients in the study. As a pragmatic trial, we are including all eligible patients followed by Penn Primary Care.

Key inclusion criteria

Eligibility Criteria: Patients with at least 2 visits in the past 2 years at a primary care practice at Penn Medicine who were born between 1945 and 1965.

Key exclusion criteria

Exclusion Criteria: Patients will be excluded if they have at least one HCV antibody test or viral load completed or if they are listed as up-to-date by health care maintenance.

Procedures

Through automated data extraction from Clarity, we will identify eligible patients, along with their primary care provider and practice. We will also categorize as MPM active users if they have sent or received a message in the last year. We will send an email to all PCPs (from primary care leadership) informing them of the HCV outreach pilot and asking them to opt-in with an email response if they are interested in the pre-order pilot. We will ask for and intend to receive a waiver of informed consent as this is low-risk, supported by operations, and we could not practicably evaluate the approaches with it. In pilot A, we will recruit 20 providers who have at least 50 patients eligible for HCV screening and agree to participate. The patients followed by those providers will be included in pilot A. All other patients will be included in pilot B. Except for the letter arm of pilot B, MPM active users will received messaging through MPM, and non-users will receive letters. Pilot A. We will randomize 20 participating providers in a 1:1 ratio to the opt-in or opt-out arms: 1.) Opt-in- Patients will receive standard messaging about the importance of HCV screening and ways that they can participate by

contacting their PCP. 2.) Opt-out- Research staff will place a pending order for patients and send an email to the provider asking to sign the order within 3 days. After signing of the order, we will send similar messaging, but also describe that the order has already been placed for them to participate with opt-out framing. Patients whose orders are not signed in 14 days will receive a letter as in Pilot A, Arm 1. We will send a follow-up message to those who do not complete testing 2 months after initial outreach. Pilot B. Patients will receive outreach by MPM or letter about the importance of HCV screening and ways to get screened through the practice. Those that are active MPM users will be randomized in a 1:5 ratio to receiving a letter or MPM as the communication modality. Among MPM users and non-users, they will be randomized in a 1:1 ratio (stratified by MPM status and assignment to letter or MPM) to the following language in the message: 1.) Usual care- Patients will receive standard messaging about HCV and ways to get screened. 2.) Behavioral science- Patients will receive messaging that incorporates behavioral science principles such as social norms, reciprocity, anticipated regret, and precommitment. We will send a follow-up message to those who do not complete testing 2 months after initial outreach.

Analysis Plan

The primary outcome will be the percentage of patients who complete HCV antibody testing within 4 months of initial outreach. We will conduct a chi-square analysis using Stata to compare Opt-in and Opt-out arms in Part A using intent-to-treat protocol. In part B, we will compare electronic messaging to letter outreach and behavioral science to usual care messaging separately.

As a secondary outcome, we will compare completion of HCV antibody testing within 12 months of initial outreach. We will also look at the percentage of tests that are positive, those with detectable viral loads, and the percentage that are referred to and receive HCV treatment and cure. We will compare response rates by MPM status, race/ethnicity, gender, and income (by zip code). Analysis will be conducted by blinded members of the research team at least four months after the initial outreach is completed for all patients.

Sample size. For pilot A, we will recruit 20 providers who have at least 50 patients eligible for HCV screening and agree to participate. They have a mean of 193 eligible patients with a standard deviation of 134, which will result in approximately 3,860 eligible patients. We estimate that standard messaging will result in a 5 percent response rate, based on findings from other screening outreach activities. Assuming a coefficient of variation of .42, we will have 90% power to detect a 7 percentage point difference (5% vs. 12%) in response rate between the opt-in and opt-out arms. This relies on estimating the harmonic mean of the number of patients per provider, which we estimated to be 114.

For pilot B, there are 26,162 remaining patients across the health system that are eligible for HCV screening. We have 90% power to detect an increase in response rate of .9 percentage points for the BE arm as compared to UC. 15,959 of the eligible patients are active MPM users, as we do not anticipate there will be interaction between messaging and modality. With a 1:5 randomization ratio of letter to MPM (approximately 2,659 receiving letters and 13,300 receiving MPM messages), we have 90% power to detect an increase in response rate of 1.6 percentage points for the MPM arm as compared to the letter arm. The 1:5 ratio was chosen to minimize resources needed to send letters, as there is an operational imperative to conduct outreach to all eligible patients across the health system.

Consent

1. Consent Process

Overview

Waiver of consent for this study will be requested. Please see below.

Children and Adolescents

Not applicable.

Adult Subjects Not Competent to Give Consent

Waiver of consent is being requested.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*

Waiver or alteration of required elements of consent.

Minimal Risk*

This study involves no more than minimal risk to subjects. Hepatitis C antibody testing is clinically available and routinely utilized to screen patients for Hepatitis C. The outreach methods in each arm are all offered during routine clinical care either at Penn Medicine or other health systems across the country. The only research related activity is the randomization of subjects to different outreach strategies that would typically occur in routine practice.

Impact on Subject Rights and Welfare*

Subjects rights and welfare will not be adversely affected by the waiver of authorization and consent. All subjects will have the opportunity to voluntarily participate in Hepatitis C screening.

Waiver Essential to Research*

We believe that we would not be able to practically conduct the research without waiver of consent. If we had to obtain either written or verbal consent ahead of time, it would substantially limit our study population and it may alter their participation in the intervention. Thus, we would only learn about the response rate for patients who we were able to speak to for consent. This, would limit the generalizability to practice. Simply waiving documentation of consent (and thus including a consent letter that does not require a subject signature) is not sufficient in this scenario. We believe that including a consent letter in the mailings could potentially bias subjects to not participate in a clinically available and indicated screening test, and it could alter their participation. Obtaining waiver of consent would allow us to avoid the potential selection/volunteer bias for inclusion of patients particularly interested in screening that can occur when consent is required. Since our main objective is to understand the potential influence varying outreach strategies on subject behavior, we believe that obtaining consent would compromise our primary objective. Additionally, we have received waiver of

consent for similar studies related to population health screening outreach.

Additional Information to Subjects

Subjects who are screened will be provided with appropriate information about positive and negative tests as is routine clinical practice.

Written Statement of Research*

No

Risk / Benefit

Potential Study Risks

The risks associated with this study are no more than minimal. There is the potential risk of breach of confidentiality. We will minimize this risk by using de-identified information whenever possible and by maintaining all identifiable information on a secure drive and/or in a HIPAA-compliant system (e.g. REDCap). There is also the risk of psychological harm associated with being screened for hepatitis. We will minimize this risk by communicating the results of the screening test to the subject in a timely fashion and facilitating the scheduling of treatment evaluation if the screening test is positive (as is usual practice for screening outreach programs).

Potential Study Benefits

If a participant completes Hepatitis C screening, which is standard clinical care, the subjects will potentially benefit from participation by increasing the chances of curing Hepatitis C at an early stage. Information learned from this study may benefit society through a better understanding of how to effectively increase overall participation rates in Hepatitis C screening which could in turn reduce the rate of liver-related mortality.

Alternatives to Participation (optional)

Data and Safety Monitoring

Safety will be overseen by the PI and the study team. In the case of possible events, the PI or designee will review the study charts to evaluate events at each subject interaction to ensure the grade, relationship to the study procedure, expectedness, and the course of action for each subject is documented.

Risk / Benefit Assessment

The risks associated with this study are no more than minimal. Better knowledge of how to increase Hepattis C screening could potentially address one of the major barriers of accessing care, i.e. having patients come in for clinical office visits. For these reasons and those outlined in the above benefits section, the investigators believes that the risks of participating in the study are outweighed by the potential benefits of participating in the study.

Final Protocol

****New changes from initial protocol notated in bold, parts removed from initial protocol notated in strikethrough**

Brief Description

This project aims to evaluate different approaches to increase Hepatitis C screening among primary care patients at Penn Medicine through a centralized screening outreach program. In a pragmatic trial, we will evaluate different approaches to increase completion of screening among eligible patients, including changing the default from opt-in to opt-out and incorporating behavioral science principles into the outreach communication.

Protocol

Abstract

Hepatitis C is treatable with effective medications, but only about half of primary care patients in the appropriate age group are up-to-date on screening. In this project, we will evaluate different ways to reach out to eligible patients to encourage them to participate in screening. Through letters and the electronic health record portal, we will compare an opt-out approach and language incorporating behavioral science principles to traditional outreach messaging with the goal of increasing Hepatitis C screening uptake.

Objectives

Overall objectives

We will develop and evaluate a centralized approach to increasing Hepatitis C screening rates through direct outreach to patients' homes. This pragmatic randomized controlled trial has the following aims: Aim 1: To compare opt-out screening outreach with a signed order to traditional opt-in screening outreach. Aim 2: Among active electronic health record portal users, to compare electronic and mailed outreach. Aim 3: To compare messaging that incorporates behavioral science principles to standard messaging about HCV screening.

Primary outcome variable(s)

The primary outcome will be the percentage of patients who complete HCV antibody testing within 4 months of initial outreach.

Secondary outcome variable(s)

Secondary outcome will be completion of HCV antibody testing within 12 months of initial outreach. We will also look at **the number of HCV screening tests ordered, the** percentage of tests that are positive, those with detectable viral loads, and the percentage that are referred to and receive HCV treatment and cure.

Background

The hepatitis C virus (HCV) is the leading cause of liver transplant and hepatocellular carcinoma in the US. New direct-acting antivirals are available that can eradicate the disease in over 95% of those that are treated, with minimal side effects. As a result of new therapies and a five-fold higher risk among baby boomers, the US Preventive Services Task Force and CDC now recommend HCV screening for all patients born between 1945 and 1965. Of the estimated 3.2 million people chronically infected with HCV, about 75% were born during this time frame. Despite this, national rates of screening among this group remain low at less than 30%. If more people could get screened, we could potentially identify more undiagnosed disease and help navigate to treatment. At Penn Medicine primary care practices, HCV screening rates have risen from 37% in 2014 to 61% in 2017, likely from a combination of provider educational efforts and EHR alerts. There is also significant practice variation ranging from 4% to 99% screening rates. While EHR alerts have been shown to increase HCV screening rates, there is potential to complement this with direct outreach to patient's homes, as has been incorporated into cancer screening initiatives. Additionally, there is a mandate from the state of Pennsylvania requiring health care providers to offer HCV testing to all primary care patients. There is an opportunity to provide direct outreach to all eligible primary care patients at Penn Medicine, while also evaluating different approaches to increasing HCV screening rates. Insights from behavioral science have been shown to increase participation in health promoting behaviors in a variety of ways. Switching from opt-in to opt-out framing has been shown to triple patient participation in remote monitoring and CRC screening. Additionally, messaging that incorporates social norms, reciprocity, and precommitment have also been shown to increase participation. However, it is not clear how these approaches would translate to HCV screening.

Study Design

Design

This is a pragmatic randomized controlled trial with two parts. **In** Pilot A **we will use patient-level randomization stratified by providers** ~~is a cluster randomized controlled trial with 1:1 randomization at the provider level~~ to **compare** an opt-in or **to** opt-out approach. Pilot B is a patient-level randomized controlled trial with factorial design. Active EHR portal patients will be randomized in a 1:5 ratio to letter or EHR messages. Additionally, all patients in part B will be randomized in a 1:1 ratio to usual care messaging or behavioral science messaging.

Study duration

We anticipate 2 months to recruit providers, identify eligible patients through electronic data extraction, and conduct initial outreach. We will then follow patients for 12 months after initial outreach. We plan to start enrollment in September 2018.

Resources necessary for human research protection

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Dr. Shivan Mehta is the PI of this study. He is a gastroenterologist and assistant professor of medicine at the Perelman School of Medicine, University of Pennsylvania. All members of the research team have completed CITI human subjects research training. Standard Operating Procedure documents for the project will be accessible to all members of the research team, which will keep research staff informed about the protocol and their related duties. There are adequate facilities to conduct the research; all research staff have adequate office space on the UPenn campus.

Characteristics of the Study Population

Target population

Primary care patients at Penn Medicine born between 1945-1965 and not up-to-date with screening for Hepatitis C.

Subjects enrolled by Penn Researchers

~~30022~~ **21,493**

Subjects enrolled by Collaborating Researchers

0

Subject Recruitment
~~30,022~~ **21,493** patients will be identified through automated data extraction from the electronic health record (EHR). All eligible patients in primary care will receive outreach through the study.

Accrual

We will conduct the study in close partnership with the Primary Care Service Line, who has agreed to include all patients in the study. As a pragmatic trial, we are including all eligible patients followed by Penn Primary Care.

Key inclusion criteria

Eligibility Criteria: Patients with at least 2 visits in the past 2 years at a primary care practice at Penn Medicine who were born between 1945 and 1965.

Key exclusion criteria

Exclusion Criteria: Patients will be excluded if they have at least one HCV antibody test or viral load completed, **if they do not have an active PCP**, or if they are listed as **having been tested elsewhere, declined screening, or are** up-to-date by health care maintenance.

Additionally, providers and patients at Lancaster General and Princeton Health systems will be excluded as they are affiliated practices with incomplete data.

Procedures

Through automated data extraction from Clarity, we will identify eligible patients, along with their primary care provider and practice. We will also categorize as MPM active users if they have sent or received a message in the last year. We will send an email to all PCPs (from primary care leadership) **that will 1)** inform~~ing~~ them of the HCV outreach pilot **and our outreach to their patients on their behalf, including use of their electronic signature,** and **2)** asking them to opt-in with an email response if they are interested in the pre-order pilot. We will ask for and intend to receive a waiver of informed consent as this is low-risk, supported by operations, and we could not practicably evaluate the approaches with it.

In pilot A, we will recruit **at least 10** ~~20~~ providers who have ~~at least~~ **between** ~~50~~ **35 and** ~~**200**~~ **250** patients eligible for HCV screening and agree to participate. The patients followed by those providers will be included in pilot A. All other patients will be included in pilot B. Except for the letter arm of pilot B, MPM active users will received messaging through MPM, and non-users will receive letters.

Pilot A.
We will randomize ~~20 participating providers~~ **patients stratified by the participating providers** in a 1:1 ratio to the opt-in or opt-out arms:
1.) Opt-in- Patients will receive standard messaging about the importance of HCV screening and ways that they can participate by contacting their PCP.
2.) Opt-out- **Credentialed clinical members of the** ~~R~~**r**esearch staff will place a**n** ~~pending~~ order for **all** patients **assigned to providers in this arm. All results will be routed through the PCP.** ~~and send an email to the provider asking to sign the order within 3 days.~~ After signing of the order, we will send **it to patients along with** similar messaging **to those in the Opt-In group,** but also describe that the order has already been placed for them to participate with opt-out framing. ~~Patients whose orders are not signed in 14 days will receive a letter as in Pilot A, Arm 1.~~

We will send a follow-up message to those who do not complete testing 2 months after initial outreach**, including another copy of the signed order** ~~**(if included in the initial outreach)**~~**. Patients in this arm who complete testing will receive a negative results letter when negative results are returned. The research team will route an encounter to the patient's Primary Care Provider if a positive result is received for a patient in this arm. The PCP will assist with care coordination and follow-up. Patient's in this arm with an invalid test result will receive a letter requesting they repeat the test, along with another copy of their signed order.**

Pilot B. Patients will receive outreach by MPM or letter about the importance of HCV screening and ways to get screened through the practice. Those that are active MPM users will be randomized in a 1:5 ratio to receiving a letter or MPM as the communication modality. Among MPM users and non-users, they will be randomized in a 1:1 ratio (stratified by MPM status and assignment to letter or MPM) to the following language in the message:

1.) Usual care- Patients will receive standard messaging about HCV and ways to get screened.
2.) Behavioral science- Patients will receive messaging that incorporates behavioral science principles such as social norms, reciprocity, anticipated regret, and pre-commitment. We will send a follow-up message to those who do not complete testing 2 months after initial outreach.

All messages, whether mailed letters or electronic MPM messages, will be generated via Epic.

Participants assigned to receive MPM messaging will be batch sent electronic messaging from a user called "Penn Primary Care" and letters will be personalized and electronically signed by their Primary Care Provider. Letters and signed lab orders that must be mailed will be "printed" to a secure .pdf file on a secure drive behind the UPHS firewall accessible by research staff. Mailed letters will also be personalized and electronically signed by the patient's PCP. Research staff will batch these letters by study arm and confirm that the appropriate letters are going to the correct participants. This file will be transferred to an outside vendor (Paradigm Digital Color) who was identified as a primary preferred vendor for large print projects for Penn Medicine by Marketing. Paradigm Digital Color has signed a Business Associates Agreement for the completion of this project and have agreed to comply with security measures identified by UPHS IS as appropriate for the transfer and protection of this data. Digital Color will print the files to be included in a window envelope so no matching between names and address on envelopes and letters will be required. For those participants in Pilot A who will receive a signed lab requisition, matching of the letter to the signed order will be required and will be completed by Digital Color using technology and human confirmation to ensure privacy. This process will be repeated with all follow-up print materials.

Results. A data pull will identify new HCV screening results for patients in the study. Positive antibody test results will be followed with a confirmatory test for HCV. Confirmed positive patients will be individually chart reviewed to identify referrals made for treatment, treatment start date, end of treatment and cure status. Some patients may be referred outside of Penn for treatment and cure and Care Everywhere encounters may be reviewed for this information.

Analysis Plan

The primary outcome will be the percentage of patients who complete HCV antibody testing within 4 months of initial outreach. We will conduct a chi-square analysis using Stata to compare Opt-in and Opt-out arms in Part A using intent-to-treat protocol. In part B, we will compare electronic messaging to letter outreach and behavioral science to usual care messaging separately.

As a secondary outcome, we will compare completion of HCV antibody testing within 12 months of initial outreach. We will also look at the **number of HCV screening tests ordered during the outreach period, the** percentage of tests that are positive, those with detectable viral loads, and the percentage that are referred to and receive HCV treatment and cure. We will compare response rates by MPM status, race/ethnicity, gender, and income (by zip code). Analysis will be conducted by blinded members of the research team at least four months after the initial outreach is completed for all patients.

Sample size. For pilot A, we will recruit ~~20~~ **at least 10** providers who have ~~at least 50~~ **between 35 and 250** patients eligible for HCV screening and agree to participate. They have a mean of ~~193~~ **116** eligible patients ~~with a standard deviation of 134~~, which will result in ~~approximately 3,860~~ **at least 1,160** eligible patients. We estimate that standard messaging will result in a 5 percent response rate, based on findings from other screening outreach activities. ~~Assuming a coefficient of variation of .42, w~~**W**e **estimate we** will have 90% power to detect a ~~7~~**5** percentage point difference (5% vs. ~~12~~**10**%) in response rate between the opt-in and opt-out arms **[power twoprop .05 .10, n(1160)]**. ~~This relies on estimating the harmonic mean of the number of patients per provider, which we estimated to be 114.~~

For pilot B, there are 26,162 remaining patients across the health system that are eligible for HCV screening. We have 90% power to detect an increase in response rate of .9 percentage points for the BE arm as compared to UC **[power twoprop .05 .059, n(26162)]**. 15,959 of the eligible patients are active MPM users, as we do not anticipate there will be interaction between messaging and modality. With a 1:5 randomization ratio of letter to MPM (approximately 2,659 receiving letters and 13,300 receiving MPM messages), we have 90% power to detect an increase in response rate of 1.6 percentage points for the MPM arm as compared to the letter arm **[power twoprop .05 .066, n1(2659) n2(13300)]**. The 1:5 ratio was chosen to minimize resources needed to send letters, as there is an operational imperative to conduct outreach to all eligible patients across the health system.

Consent

1. Consent Process

Overview

Waiver of consent for this study will be requested. Please see below.

Children and Adolescents

Not applicable.

Adult Subjects Not Competent to Give Consent

Waiver of consent is being requested.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*

Waiver or alteration of required elements of consent.

Minimal Risk*

This study involves no more than minimal risk to subjects. Hepatitis C antibody testing is clinically available and routinely utilized to screen patients for Hepatitis C. The outreach methods in each arm are all offered during routine clinical care either at Penn Medicine or other health systems across the country. The only research related activity is the randomization of subjects to different outreach strategies that would typically occur in routine practice.

Impact on Subject Rights and Welfare*

Subjects rights and welfare will not be adversely affected by the waiver of authorization and consent. All subjects will have the opportunity to voluntarily participate in Hepatitis C screening.

Waiver Essential to Research*

We believe that we would not be able to practically conduct the research without waiver of consent. If we had to obtain either written or verbal consent ahead of time, it would substantially limit our study population and it may alter their participation in the intervention. Thus, we would only learn about the response rate for patients who we were able to speak to for consent. This, would limit the

generalizability to practice. Simply waiving documentation of consent (and thus including a consent letter that does not require a subject signature) is not sufficient in this scenario. We believe that including a consent letter in the mailings could potentially bias subjects to not participate in a clinically available and indicated screening test, and it could alter their participation. Obtaining waiver of consent would allow us to avoid the potential selection/volunteer bias for inclusion of patients particularly interested in screening that can occur when consent is required. Since our main objective is to understand the potential influence varying outreach strategies on subject behavior, we believe that obtaining consent would compromise our primary objective. Additionally, we have received waiver of consent for similar studies related to population health screening outreach.

Additional Information to Subjects

Subjects who are screened will be provided with appropriate information about positive and negative tests as is routine clinical practice.

Written Statement of Research*

No

Risk / Benefit

Potential Study Risks

The risks associated with this study are no more than minimal. There is the potential risk of breach of confidentiality. We will minimize this risk by using de-identified information whenever possible and by maintaining all identifiable information on a secure drive and/or in a HIPAA-compliant system (e.g. REDCap). There is also the risk of psychological harm associated with being screened for hepatitis. We will minimize this risk by communicating the results of the screening test to the subject in a timely fashion and facilitating the scheduling of treatment evaluation if the screening test is positive (as is usual practice for screening outreach programs).

Potential Study Benefits

If a participant completes Hepatitis C screening, which is standard clinical care, the subjects will potentially benefit from participation by increasing the chances of curing Hepatitis C at an early stage. Information learned from this study may benefit society through a better understanding of how to effectively increase overall participation rates in Hepatitis C screening which could in turn reduce the rate of liver-related mortality.

Alternatives to Participation (optional)

Data and Safety Monitoring

Safety will be overseen by the PI and the study team. In the case of possible events, the PI or designee will review the study charts to evaluate events at each subject interaction to ensure the grade, relationship to the study procedure, expectedness, and the course of action for each subject is documented.

Risk / Benefit Assessment

The risks associated with this study are no more than minimal. Better knowledge of how to increase

Hepattis C screening could potentially address one of the major barriers of accessing care, i.e. having patients come in for clinical office visits. For these reasons and those outlined in the above benefits section, the investigators believes that the risks of participating in the study are outweighed by the potential benefits of participating in the study.

Summary of Protocol Changes Modifications LOG

Protocol: Behavioral Science and Hepatitis C Screening Outreach Among Primary Care Patients
University of Pennsylvania Principal Investigator: Shivan Mehta, MD

Date of Submission	Description of Modification	Rationale for Modification	Approval date
09/14/2018	Initial submission		09/19/2018
1/25/2019	1) Updating patient message content 2) Updating patient messaging procedures 3) Adding messaging for providers 4) Add staff	1) Reference to state/local screening guidelines; vetting by key stakeholders 2) EHR to generate all messages so documentation included in patient chart; print vendor for size/scale of project as well as for future outreach to patients who cannot or do not use the patient portal. 3) Notifications to all primary care providers informing them of the project; signed by primary care leadership 4) Add Jessica Sung, research coordinator	02/04/2019
02/25/2019	1) Updating patient message content 2) Updating order/requisition procedures 3) Updating provider message content	1) Reduced average reading grade level from grade 10.4 to 8.2 for improved readability 2) Updated procedures for placing bulk orders by credentialed members of study team without burdening PCP for signing pended orders 3) Clarified provider vs. study team responsibilities	02/27/2019
03/14/2019	1) Update key exclusion criteria 2) Update subject recruitment 3) Update procedures – randomization 4) Update power/sample size calculations and analysis plan	1) Exclude affiliated health system patients because practices have incomplete data and are not fully integrated with central EHR; patients who have indicated prior testing or declined screening excluded since mandate to notify has been met. 2) Sample size reduced after updating exclusion criteria 3) Patient-level randomization more appropriate than previously planned provider level cluster randomization. 4) New randomization procedure increases power to detect a smaller but still clinically significant difference between groups.	03/19/2019
07/19/2019	1) Add staff	1) Add Caitlin McDonald, research coordinator	07/24/2019

09/27/2019	1) Clarify earlier study design change 2) Clarify analysis plan	1) In an earlier amendment (3/14/19) we updated randomization procedures for Pilot A from cluster randomization at the provider level to patient level randomization stratified by providers. This section was missed in that update. 2) Revisit outcomes and provide more detailed/thorough analysis plan to ensure completeness. Updated to include number of HCV screening tests ordered during intervention period.	09/30/2019
7/13/2020	1) Clarify use of Care Everywhere	1) Confirmed positive patients will be chart reviewed to identify referrals made for treatment, treatment start date, end of treatment and cure status. Some patients may be referred outside of Penn for treatment and cure and Care Everywhere encounters may be reviewed for this information.	7/15/2020

Initial Statistical Analysis Plan

Analysis Plan

The primary outcome will be the percentage of patients who complete HCV antibody testing within 4 months of initial outreach. We will conduct a chi-square analysis using Stata to compare Opt-in and Opt-out arms in Part A using intent-to-treat protocol. In part B, we will compare electronic messaging to letter outreach and behavioral science to usual care messaging separately.

As a secondary outcome, we will compare completion of HCV antibody testing within 12 months of initial outreach. We will also look at the percentage of tests that are positive, those with detectable viral loads, and the percentage that are referred to and receive HCV treatment and cure. We will compare response rates by MPM status, race/ethnicity, gender, and income (by zip code). Analysis will be conducted by blinded members of the research team at least four months after the initial outreach is completed for all patients.

Sample size. For pilot A, we will recruit 20 providers who have at least 50 patients eligible for HCV screening and agree to participate. They have a mean of 193 eligible patients with a standard deviation of 134, which will result in approximately 3,860 eligible patients. We estimate that standard messaging will result in a 5 percent response rate, based on findings from other screening outreach activities. Assuming a coefficient of variation of .42, we will have 90% power to detect a 7 percentage point difference (5% vs. 12%) in response rate between the opt-in and opt-out arms. This relies on estimating the harmonic mean of the number of patients per provider, which we estimated to be 114.

For pilot B, there are 26,162 remaining patients across the health system that are eligible for HCV screening. We have 90% power to detect an increase in response rate of .9 percentage points for the BE arm as compared to UC. 15,959 of the eligible patients are active MPM users, as we do not anticipate there will be interaction between messaging and modality. With a 1:5 randomization ratio of letter to MPM (approximately 2,659 receiving letters and 13,300 receiving MPM messages), we have 90% power to detect an increase in response rate of 1.6 percentage points for the MPM arm as compared to the letter arm. The 1:5 ratio was chosen to minimize resources needed to send letters, as there is an operational imperative to conduct outreach to all eligible patients across the health system.

Final Statistical Analysis Plan

****New changes from initial protocol notated in bold, parts removed from initial protocol notated in strikethrough**

Analysis Plan

The primary outcome will be the percentage of patients who complete HCV antibody testing within 4 months of initial outreach. We will conduct a chi-square analysis using Stata to compare Opt-in and Opt-out arms in Part A using intent-to-treat protocol. In part B, we will compare electronic messaging to letter outreach and behavioral science to usual care messaging separately.

As a secondary outcome, we will compare completion of HCV antibody testing within 12 months of initial outreach. We will also look at the **number of HCV screening tests ordered during the outreach period, the** percentage of tests that are positive, those with detectable viral loads, and the percentage that are referred to and receive HCV treatment and cure. We will compare response rates by MPM status, race/ethnicity, gender, and income (by zip code). Analysis will be conducted by blinded members of the research team at least four months after the initial outreach is completed for all patients.

Sample size. For pilot A, we will recruit ~~20~~ **at least 10** providers who have ~~at least 50~~ **between 35 and 250** patients eligible for HCV screening and agree to participate. They have a mean of ~~193~~ **116** eligible patients ~~with a standard deviation of 134~~, which will result in ~~approximately 3,860~~ **at least 1,160** eligible patients. We estimate that standard messaging will result in a 5 percent response rate, based on findings from other screening outreach activities. ~~Assuming a coefficient of variation of .42, w~~**We estimate we** will have 90% power to detect a ~~7~~**5** percentage point difference (5% vs. ~~12~~**10**%) in response rate between the opt-in and opt-out arms **[power twoprop .05 .10, n(1160)]**. ~~This relies on estimating the harmonic mean of the number of patients per provider, which we estimated to be 114.~~

For pilot B, there are 26,162 remaining patients across the health system that are eligible for HCV screening. We have 90% power to detect an increase in response rate of .9 percentage points for the BE arm as compared to UC **[power twoprop .05 .059, n(26162)]**. 15,959 of the eligible patients are active MPM users, as we do not anticipate there will be interaction between messaging and modality. With a 1:5 randomization ratio of letter to MPM (approximately 2,659 receiving letters and 13,300 receiving MPM messages), we have 90% power to detect an increase in response rate of 1.6 percentage points for the MPM arm as compared to the letter arm **[power twoprop .05 .066, n1(2659) n2(13300)]**. The 1:5 ratio was chosen to minimize resources needed to send letters, as there is an operational imperative to conduct outreach to all eligible patients across the health system.

Summary of Statistical Analysis Plan Modifications

Before beginning any analysis, we felt it necessary to revisit outcomes and provide a more detailed/thorough analysis plan to ensure both were as complete as possible.

Appendix A

Participant and Provider Messaging Content

Arms: A1, B1, B5 - Usual Care Initial Letters

<PCP Name>
<PCP Office Address>

<Date>

<Patient Name>
<Patient Address>

Dear <Patient Name>,

In the past few years, a safer and better treatment for Hepatitis C, a serious infection that can lead to liver disease, has become available. Over half of people who have Hepatitis C do not know it and do not look or feel sick.

The US Preventive Task Force recommends testing for all patients born between 1945 and 1965, even if no risk factors are present. Other local and national guidelines also recommend Hepatitis C testing for everyone born during this time.

We noticed that you were born within this time, but we have no record that you have been tested for Hepatitis C.

If you would like to be tested for Hepatitis C, which involves only a simple blood test, please call the office at <office phone number> or let us know at your next visit that you would like to be tested. If you have already been tested for Hepatitis C, please let us know and we will update your records.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

Arms A1, B1, B5: Usual Care Reminder Letters

<PCP Name>
<PCP Office Address>

<Date>

<Patient Name>
<Patient Address>

Dear <Patient Name>,

A few weeks ago, we sent you a letter about the importance of getting tested for Hepatitis C, a serious infection that can lead to liver disease. Local and national guidelines recommend Hepatitis C testing for everyone born between 1945 and 1965. To date, we have no record that you have been tested.

If you would like to be tested for Hepatitis C, which involves only a simple blood test, please call the office at <office phone number> or let us know at your next visit that you would like to be tested. If you have already been tested for Hepatitis C, please let us know and we will update your records.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

Arms B2, B6 – Behavioral Content Initial Letters

<PCP Name>

<PCP Office Address>

<Date>

<Patient Name>
<Patient Address>

Dear <Patient Name>,

Over half of people who have Hepatitis C do not know it and do not look or feel sick, and patients born between 1945 and 1965 are at highest risk. Now that there are simple and effective cures for Hepatitis C, testing is important to prevent serious illness caused by this infection such as liver failure and liver cancer.

The US Preventive Task Force recommends testing for all patients born between 1945 and 1965, even if no risk factors are present. Other local and national guidelines also recommend Hepatitis C testing for everyone born during this time.

We noticed that you were born within this time, but we have no record that you have been tested for Hepatitis C.

If you would like to be tested for Hepatitis C, please call the office at <office phone number> or let us know at your next visit that you would like to be tested.

For your health, we are asking that you:

- **Get tested early for Hepatitis C, which can lower your risk of getting liver disease later in life.**
- **Help us reach our goal of having 100% of patients tested at Penn Medicine.**
- **Write down a date that you will have your testing completed by: _____**

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

If you have already been tested for Hepatitis C, please let us know and we will update your records. You can call the office at <office phone number> or inform us at your next visit.

Here's a chance to join the majority of others at Penn Medicine who have already been tested for Hepatitis C. It's easy, and it's something you can do for both you and your family.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,

<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

B2, B6: Behavioral Content Reminder Letters

<PCP Name>
<PCP Office Address>

<Date>

<Patient Name>
<Patient Address>

Dear <Patient Name>,

A few weeks ago, we sent you a letter about the importance of getting tested for Hepatitis C. Now that there are simple and effective cures for Hepatitis C, testing is important to prevent serious illness caused by this infection such as liver failure and liver cancer. Local and national guidelines recommend Hepatitis C testing for everyone born between 1945 and 1965. To date, we have no record that you have been tested.

For your health, we are asking that you:

- **Get tested early for Hepatitis C, which can lower your risk of getting liver disease later in life.**
- **Help us reach our goal of having 100% of patients tested at Penn Medicine.**
- **Write down a date that you will have your testing completed by: _____**

If you would like to be tested for Hepatitis C, please call the office at <office phone number> or let us know at your next visit that you would like to be tested.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

If you have already been tested for Hepatitis C, please let us know and we will update your records. You can call the office at <office phone number> or inform us at your next visit.

Here's a chance to join the majority of others at Penn Medicine who have already been tested for Hepatitis C. It's easy, and it's something you can do for both you and your family.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine, University of Pennsylvania

A2: Usual Care Initial Letter + Order

<PCP Name>
<PCP Office Address>

<Date>

<Patient Name>
<Patient Address>

Dear <Patient Name>,

In the past few years, a safer and better treatment for Hepatitis C, a serious infection that can lead to liver disease, has become available. Over half of people who have Hepatitis C do not know it and do not look or feel sick.

The US Preventive Task Force recommends testing for all patients born between 1945 and 1965, even if no risk factors are present. Other local and national guidelines also recommend Hepatitis C testing for everyone born during this time.

We noticed that you were born within this time, but we have no record that you have been tested for Hepatitis C.

We have placed an order for your Hepatitis C testing. Please take the enclosed order for a simple blood test to either a Penn Medicine lab or any lab is covered by your health insurance.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

If you have already been tested for Hepatitis C, please let us know and we will update your records. You can call the office at <office phone number> or inform us at your next visit.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

A2: Usual Care Reminder Letter + Order

<PCP Name>
<PCP Office Address>

<Date>

<Patient Name>
<Patient Address>

Dear <Patient Name>,

A few weeks ago, we sent you a letter about the importance of getting tested for Hepatitis C, a serious infection that can lead to liver disease. Local and national guidelines recommend Hepatitis C testing for everyone born between 1945 and 1965. To date, we have no record that you have been tested.

We have placed an order for your Hepatitis C testing. Please take the enclosed order for a simple blood test to either a Penn Medicine lab or whichever lab is covered by your health insurance. If you have already been tested for Hepatitis C, please let us know and we will update your records.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

B3 – Usual Care Initial Patient Portal Messaging

Dear <Patient Name>,

In the past few years, a safer and better treatment for Hepatitis C, a serious infection that can lead to liver disease, has become available. Over half of people who have Hepatitis C do not know it and do not look or feel sick.

The US Preventive Task Force recommends testing for all patients born between 1945 and 1965, even if no risk factors are present. Other local and national guidelines also recommend Hepatitis C testing for everyone born during this time.

We noticed that you were born within this time but, we have no record that you have been tested for Hepatitis C.

If you would like to be tested for Hepatitis C, which involves only a simple blood test, please do one of the following:

1) Send us a message through "Contact Your Care Team" on myPennMedicine so this test can be ordered.
2) Let us know at your next visit that you would like to be tested.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

If you have already been tested for Hepatitis C, please let us know and we will update your records. You can send a message through "Contact Your Care Team" on myPennMedicine, call the office at <office phone number> or inform us at your next visit.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

B3: Usual Care Reminder Patient Portal Messaging

Dear <Patient Name>,

A few weeks ago, we sent you a message about the importance of getting tested for Hepatitis C, a serious infection that can lead to liver disease. Local and national guidelines recommend Hepatitis C testing for everyone born between 1945 and 1965. To date, we have no record that you have been tested.

If you would like to be tested for Hepatitis C, please do one of the following:

1) Send us a message through "Contact Your Care Team" on myPennMedicine so this test can be ordered.
2) Let us know at your next visit that you would like to be tested.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert in Hepatitis C at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

If you have already been tested for Hepatitis C, please let us know and we will update your records. You can send a message through "Contact Your Care Team" on myPennMedicine, call the office at <office phone number> or inform us at your next visit.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

B4: Behavioral Content Initial Patient Portal Messaging

Dear <Patient Name>,

Over half of people who have Hepatitis C do not know it and do not look or feel sick, and patients born between 1945 and 1965 are at highest risk. Now that there are simple and effective cures for Hepatitis C, testing is important to prevent serious illness caused by this infection such as liver failure and liver cancer.

The US Preventive Task Force recommends testing for all patients born between 1945 and 1965, even if no risk factors are present. Other local and national guidelines also recommend Hepatitis C testing for everyone born during this time.

We noticed that you were born within this time, but we have no record that you have been tested for Hepatitis C.

For your health, we are asking that you:

- **Get tested early for Hepatitis C, which can lower your risk of getting liver disease later in life.**
- **Help us reach our goal of having 100% of patients tested at Penn Medicine.**
- **Write down a date that you will have your testing completed by: _____**

If you would like to be tested for Hepatitis C, please do one of the following:

1) Send us a message through "Contact Your Care Team" on myPennMedicine so this test can be ordered.
2) Let us know at your next visit that you would like to be tested.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see an expert somewhere else, we can help you.

If you have already been tested for Hepatitis C, please let us know and we will update your records. You can send a message through "Contact Your Care Team" on myPennMedicine, call the office at <office phone number> or inform us at your next visit.

Here's a chance to join the majority of others at Penn Medicine who have already been tested for Hepatitis C. It's easy, and it's something you can do for both you and your family.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine

B4: Behavioral Content Reminder Patient Portal Messaging

Dear <Patient Name>,

A few weeks ago, we sent you a message about the importance of getting tested for Hepatitis C. Now that there are simple and effective cures for Hepatitis C, testing is important to prevent serious illness caused by this infection such as liver failure and liver cancer. Local and national guidelines recommend Hepatitis C testing for everyone born between 1945 and 1965. To date, we have no record that you have been tested.

For your health, we are asking that you:

- **Get tested early for Hepatitis C, which can lower your risk of getting liver disease later in life.**
- **Help us reach our goal of having 100% of patients tested at Penn Medicine.**
- **Write down a date that you will have your testing completed by: _____**

If you would like to be tested for Hepatitis C, please do one of the following:

1) Send us a message through "Contact Your Care Team" on myPennMedicine so this test can be ordered.
2) Let us know at your next visit that you would like to be tested.

Once tested, we will tell you your results. If you have Hepatitis C, you will be referred to an expert at Penn Medicine for treatment. If you prefer to see a specialist somewhere else, we can help you.

If you have already been tested for Hepatitis C, please let us know and we will update your records. You can send a message through "Contact Your Care Team" on myPennMedicine, call the office at <office phone number> or inform us at your next visit

Here's a chance to join the majority of others at Penn Medicine who have already been tested for Hepatitis C. It's easy, and it's something you can do for both you and your family.

To learn more about Hepatitis C, go to: www.PennMedicine.org/HepatitisC

Sincerely,
<PCP Signature>
<PCP Name, Degree>
Primary Care Provider
Penn Medicine