PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

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PROTOCOL TITLE

mFOCUS (multilevel FOllow-up of Cancer Screening), RCT

FUNDING

NCI (U01CA225451)

VERSION DATE

January 6, 2023

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Specific Aim 1: To evaluate the *effectiveness* of the system, team and individual components of mFOCUS vs. standard care by conducting a 4-arm cluster randomized controlled trial (RCT) of individuals who are due for follow-up of an abnormal cancer screening test. Standard care consists of well-characterized existing decision support and systems for follow-up in these three participating primary care networks and their affiliated integrated delivery systems (Brigham and Women's Hospital and Massachusetts General Hospital, both members of Partners HealthCare System, Massachusetts's largest integrated health care delivery system, and Dartmouth Hitchcock Health, the largest health care provider in New Hampshire). The primary outcome will be whether an individual receives follow-up, defined based on the type of screening abnormality and organ type, within 120 days of becoming eligible for mFOCUS. Secondary comparisons will assess multi- and cross-level (individual, team, system) outcomes**.** Because the Coronavirus pandemic impacted access to health care, we will also assess whether an individual receives follow-up, defined based on the type of screening abnormality and organ type, within 240 days of becoming eligible for mFOCUS. The study design will allow us to examine the marginal effectiveness of system, team and individual-level enhancements, and exploratory analyses will address subgroups defined by race/ ethnicity, socioeconomic status and cancer type.

Hypothesis: mFOCUS will significantly increase the proportion of individuals who receive follow-up testing, thereby reducing time to follow-up vs. standard care.

Specific Aim 2: To evaluate facilitators and barriers to the *Reach, Adoption, Implementation and Maintenance* of mFOCUS at participating primary care practice sites affiliated with three primary care networks The impact of any intervention depends on its ability to be implemented in clinical practice.

Hypothesis (***Reach***): Individuals who are due for follow-up can be reached by mFOCUS irrespective of patient sociodemographic characteristics and "severity" of the screening result. Patient surveys will be used to examine barriers and facilitators.

Hypothesis (Adoption, Implementation, and Maintenance): mFOCUS will be *adopted* across providers/ practices and consistently *implemented*. Provider and system-level surveys will be used to examine barriers and facilitators to adoption, implementation and maintenance.

NOTE: This protocol involves patients who receive care at Partners (MGH and BWH) as well as Dartmouth. Dartmouth is the relying site on the Partners IRB review a SmartIRB reliance agreement has been put in place

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

In the United States (US), most cancer screening is initiated in primary care settings but requires care transitions with other providers who either perform the test or evaluate the result. Screening benefits are only realized through timely follow-up of abnormal breast, cervical, colorectal and lung screening results. Incomplete follow-up represents an ongoing challenge as the initial screening event transitions to diagnostic evaluations involving complex interactions among patients, primary care providers (PCPs), and specialists.

Our recent study within the NCI-funded Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR) consortium reported significant rates of screening abnormalities that required additional evaluation, including; 11% of breast cancer, 8% of cervical and 5% of fecal occult blood test (FOBT)/ fecal immunochemical test (FIT) screens, consistent with other studies. The abnormality rates for colonoscopy screening (~20% adenomas) and lung cancer screening with low dose computed tomography (LDCT)'s are also high (~25%). Our work also demonstrates wide variation in follow-up rates across primary care clinics, that differ by cancer type as well as the "severity" of the screening abnormality (5 – 95% with an average of ~ 50% overall). Apart from the

legislated requirement for radiologists to follow-up abnormal mammograms, responsibility for comprehensive screening follow-up falls to the ordering provider, typically a primary care provider (PCP). Unfortunately, few PCPs/ primary care practices have systems to track abnormalities and promote follow-up. PCPs face the challenge of responsibility for managing the diagnostic evaluation for populations of patients for each of these cancers, each with differing requirements and timeframes for completion.

Barriers to follow-up of "abnormal screens" exist at individual patient and provider levels as well as at patient's care team and health system levels. Providing high-quality care for abnormal screens requires establishing new processes to systematically identify abnormal results, notify patients and providers, address barriers, and track completion of the diagnostic work-up. We propose to develop, test and disseminate a health information technology (IT)-enabled, multilevel, stepped care intervention grounded in primary care, mFOCUS (multilevel FOllowup of Cancer Screening) for abnormal breast, cervical, colorectal and lung screens. Comprehensive intervention to promote follow-up needs to be based in primary care as PCPs holistically approach each patient's needs and coordinate care among specialists. Key mFOCUS components include: system design to promote identification/tracking using an electronic health record (EHR)-integrated population management platform with education to promote culture change around the management of abnormal screens; use of individual patient and PCP reminders and tools; and a stepped-care team-level enhancement with increasing intensity of contact (i.e., administrative support and patient navigation).

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Specific Aim 1: To evaluate the *effectiveness* of the system, team and individual components of mFOCUS vs. standard care by conducting a 4-arm cluster randomized controlled trial (RCT) of individuals who are due for follow-up of an abnormal screen.

Inclusion criteria: Individuals who have an abnormal screen that is due for follow-up including:

- Breast: women 40-80 years with an *incident* (i.e., newly detected) abnormal screening mammogram or digital breast tomosynthesis (DBT) exam.
- Cervical: women 21-65 years with an *incident* abnormal screening Pap.

- Colorectal: adults 40-80 years with an abnormal screen, including *incident* FOBT/ FIT, or *prevalent* colonoscopy. Because of the long periods of time required for follow-up of colonoscopies, we will look back over a 5-year period and will therefore find *prevalent* abnormalities that become due for follow-up.
- Lung: adults 55-80 years, current and former smokers, with an *incident* abnormal LDCT result.

Definition of the specific screening abnormalities and timing of diagnostic evaluation are based on our prior work, expert opinion, and the literature. Need for follow-up will be determined by the lack of an appropriate clinical test within the specified time as documented in the EHR.

Exclusion criteria: We will exclude patients who: 1) are not English or Spanish-speaking, or 2) have had prior cancer of the organ for each screening test (i.e., women with prior breast cancer will not be tracked for breast cancer screening abnormalities) as these individuals may have non-standard follow-up care recommendations.

Intervention Design and Randomization Scheme. We will perform a 4-arm cluster RCT with randomization done at the practice-level, across the participating practices. We have chosen this level of randomization as it would be logistically complicated for the practices to have different patients randomized to different intervention components (i.e., reduced contamination). While we have received the approval of the primary care network leadership of the participating networks and have discussed the study with practice leadership, practices will be given the opportunity to opt-out of the study before practices are randomized. Randomization will be stratified based on: (1) practice size, (2) percent female, and (3) percent of patients on Medicaid as a marker for socioeconomic status.

The 4-arm design will allow us to compare "standard care" (Arm 1) to three intervention arms that represent the sequential/ stepped addition of: (Arm 2) a system-level, visit-based intervention consisting of PCP facing reminders deployed when a patient is overdue for follow-up (health maintenance reminders; automated problem list additions); (Arm 3) the addition of a population-based intervention with study staff administration of the patient and PCP facing reminders deployed when a patient is overdue for follow-up regardless of whether they come in for a visit (e.g. bulk In-Basket messaging to the PCP, Patient Gateway reminders or letters, a brief phone call or voice message for the patient); and (Arm 4) the addition of a team-level intervention including phone calls from an outreach coordinator and a patient navigator. Part of the role of the Patient Navigator will be to assess a patient's social determinants of health. If the patient has any needs the patient navigator will use "Aunt Bertha" an online platform to help patients find social services in their area. Patients in Arm 1 will receive the usual care provided by their PCP. Given our stepped care approach, this randomization

scheme will allow us to compare the cumulative addition of each level of intervention to standard care as well as the marginal effect of each additional level to the prior group. This design allows us to evaluate changing the responsibility for "opportunistic" follow-up, typically by the PCP at the time of a visit (Arm 1), to a systematic, multilevel approach, examining the cumulative and marginal effects of each subsequent level of intervention. In addition to the multilevel components, the individual- and team-level engagement algorithm will take a "stepped care" approach with increasing level of intensity of engagement.

Recruitment and Enrollment. Key organizational components of the study will involve:

(1) Practice and Provider Engagement. We have obtained support of network leadership for the study. Investigators have/ will attend practice meetings at intervention sites to integrate work flow with practice routines and educate staff about the study and its procedures. PCPs will not be required to do recruitment; identification of eligible patients will be done centrally using the IT platform described above. We therefore anticipate a high level of practice and PCP participation since the intervention does not constrain usual practice, but adds additional systems beyond those currently available. As noted above, practices and providers will be given the opportunity to opt-out of the study before practices are randomized.

(2) Patient Identification and Enrollment. The mFOCUS platform will incorporate algorithms to identify eligible patients and patient-practice attribution. All patients will remain under the direction of their personal PCP/ practice and the intervention components will facilitate the delivery of care in addition to the current standard of care.

We plan to enroll 3324 eligible participants (approximately 831/ arm – as randomization will be done at the practice level the arms will not be the same size) across the 3 participating primary care networks (BWH, MGH, and Dartmouth). We anticipate that recruitment will be somewhat higher at BWH and MGH than Dartmouth as the networks are bigger. Because randomization will be done at the practice level, we will not be able to recruit exactly 3324 individuals (patients will be in process of recruitment since they will be recruited in batches) – this is the number suggested by our sample size calculation. We anticipate that this calculations will need to be updated due to the impact of COVID-19 and that our recruitment number will be higher because of the back log of testing that will occur as hospitals reopen for screening procedures. We anticipate that we could possibly enroll up to 9,000 eligible patients at MGHBWH, and 12,000 eligible patients study wide. We will not exceed recruitment of 12,000 eligible individuals. Due to the way our IT system is configured, we anticipate that we could review up to 20,000 patient charts study wide. Not all of the patient charts reviewed will be deemed eligible.

Any patient contact (outreach coordinator, patient navigator) will be done by staff at the respective patient care sites (Partners staff will contact Partners' patients and Dartmouth staff will contact Dartmouth patients). Dependent upon randomization, patients will receive a patient gateway message (if patient has an account) or mailed letter and a phone call from a study coordinator. Patients in study arm 4 will receive patient navigation, which may involve multiple contacts by phone and/or the by a telehealth Partners approved platform.

(3) Surveys: Some of the outcomes of the study will be measured by PCP and patient surveys:

PCP Surveys: We developed brief, self-administered survey instruments to be administered to PCPs just before the trial is launched and 3 months after recruitment ends.

PCPs will be sent an introductory email from the clinical director of each primary care network. This will be followed by an email from the study investigators that explains the study purpose and opportunities to opt out/ participate of the survey. The second email will include a unique url for the PCP to use to connect to a RedCap version of the survey. PCP surveys will be administered using RedCap (up to 5 email contacts with a RedCap link over 4 weeks).

Patient surveys: We will randomly sample 15% of participants. Patient surveys will be administered 4-12 weeks after their individual follow-up period has been completed, so surveys will be conducted throughout the enrollment period. Patients will be sent an introductory letter from the clinical director of each primary care network paired with a letter from the study investigators that explains the study purpose and opportunities to opt out/ participate of the survey. The second letter will include a unique url/QR code for the patient to use to connect to a RedCap version of the survey. If patients do not opt-out within 2 weeks or complete the survey using the RedCap link provided in the letter, they will be contacted by phone and asked to complete the survey by phone or RedCap. If the patients opt for the later, they will be asked for permission to receive the survey link via un-encrypted email (and asked for the email where they would like to receive it).

Summary of primary and secondary outcome measures

Measures (data source)	
Primary outcome: Completion of follow-up within 120 days of eligibility for mFOCUS (EHR/ claims)	Patient-Reported Assessment of: *Individual-PCP:* Satisfaction with care provided by PCP
Secondary outcomes: Completion of follow-up within 240 days of eligibility for mFOCUS (EHR/ claims)	*Care Team:* Satisfaction with care provided by care team *System:* Receipt of reminder letters, calls, or emails

# of days to completion of required diagnostic evaluation (EHR/ claims)

Satisfaction with follow-up care (patient survey)

Knowledge of test result and need for follow-up (patient survey)

Satisfaction with ability of patients to get timely follow-up (PCP survey)

Time required for management (PCP survey)

PCP-Reported Assessment of:

Individual-Patient: Patient understanding of need for follow-up

Care Team: Satisfaction with coordination of care

System: Satisfaction with IT functionality to support follow-up

Analysis Plan/ Sample Size. Our primary analysis will be intention-to-treat (ITT). All eligible, enrolled patients will be part of the ITT cohort. We expect that a small number of patients may change primary care clinics within our systems. These individuals will be evaluated according to their initial intervention status. Prior to analysis, all data will be examined for accuracy, logical consistency and missing data. We expect complete data for intervention status and our outcomes. We will use multiple imputation, using the MI procedure in SAS, to account for any missing values of covariates. Through the stratified randomization we will attempt to balance patient, provider and practice characteristics between study groups. However, since randomization occurs at the practice level, we will be cautious and still compare the patient, provider and practice characteristics using Fisher exact tests, t-tests and Wilcoxon tests as appropriate to the covariate distribution. Any characteristics that show substantial clinical or statistical difference ($p<.05$) will be entered into the regression model and retained as covariates if they alter the effect estimate of the intervention by >20%.

The primary analysis model will be a random effects logistic regression, implemented through the SAS Glimmix procedure. Timely follow-up (yes/no) will be the patient-level outcome and random effects for practice and physician will allow for exchangeable correlation between patients seen within the same practice and by the same physician. The primary fixed predictors will be 3 indicator variables representing the 3 intervention arms and we will use a global likelihood ratio test to compare the 4 study arms. If the global test is significant ($p<0.05$), we will compare the intervention arms to the control group (our primary comparisons with a Bonferroni-adjusted significance level of 0.0167) and to each other (secondary comparisons). Comparisons to the control arm will capture the cumulative effects of the interventions, while comparisons between the intervention arms will capture the marginal effects of each level of intervention. We will include covariates for the type of cancer, level of initial screening abnormality, and any patient, provider or practice characteristics which are identified as confounders.

Results will be presented as adjusted follow-up rates, with 95% confidence intervals, calculated using marginal standardization.

Secondary analyses will model time-to-follow-up, using a clustered proportional hazards regression to examine whether abnormal screens are followed-up as quickly as possible. Patient-level time-to-follow-up will be recorded with censoring at the end of study for patients who never received follow-up. Patients will be clustered within providers using the generalized estimating equation approach, implemented as a "frailty" analysis in the SAS Phreg procedure. An additional correlation component for patients within practices cannot be included, but we will evaluate the robustness of our findings by using an alternative model, clustering by practice rather than provider. Predictors and covariates in this model will be identified in the same way as described above. The proportional hazards assumption for the intervention effects will be verified by entering a time-varying version of those predictors. Other secondary outcomes based on patient, provider and team surveys will use clustered linear regression models to compare satisfaction scores between study arms. Our secondary system outcome: the number of patient contacts; will be compared between arms using clustered Poisson regression. The model building will be analogous to the approach detailed above.

We will also consider several exploratory analyses. In particular, we will perform our primary and secondary analyses within each of the four types of cancer and by risk of cancer. Prior to any of these subgroup analyses, we will put the appropriate interaction terms into the primary models above. However, it was not practical to design this study to have sufficient power to pursue all of these possibilities. Instead, any "findings" in these secondary analyses will be considered as clues to be pursued in future studies and in alternative databases.

Finally, while it would be clinically important to pursue cancer detection rates, we will not do so here because we lack statistical power and because of the possibility that more cancers may be diagnosed in the intervention arms than the control arm because of higher follow-up rates with more diagnostic evaluations. We will not have long enough follow-up times to look at differences in cancer incidence related to inadequate follow-up. Instead we will perform descriptive analyses within each study arm to look at the number of incident cancers identified.

Our sample size calculation was based on an increase in the follow-up test completion rate of 11-14% with the intervention– this would give us 80% power to detect an 11% difference in the follow-up rate. We have an adequate number of potential participants across our sites to achieve this sample size.

Specific Aim 2: To evaluate facilitators and barriers to the *Reach, Adoption, Implementation and Maintenance* of mFOCUS.

The RE-AIM framework (Reach, Effectiveness, Adoption, Implementation and Maintenance with Effectiveness assessed in **Aim 2**) will allow us to assess the multilevel implementation of our intervention. The primary goal is to inform and facilitate dissemination of the program in the 3 networks rather than to test specific hypotheses. We will calculate summary statistics and conduct bivariate comparisons across sites using Fisher's exact test, t-tests, and the Wilcoxon rank sum test where applicable for survey outcomes.

RE-AIM Metric	Measure	Data Source
Reach	• % of eligible individuals in each intervention group who engage in relevant step (open email reminder, speak with outreach coordinator or PN)	• Population management system
	• Patient barriers and facilitators of follow-up	• Patient survey
Adoption	• Barriers and facilitators to follow-up • Systems & processes for follow-up • Knowledge of and satisfaction with components of mFOCUS	• PCP survey
Implementation	• Technical and organizational barriers to implementation • Fidelity of delivery of the intervention	• PCP survey • Population management system
Maintenance	• Technical and organizational barriers to maintenance	• PCP surveys

Patient, and provider surveys are attached. Once the final version of the patient survey is approved it will be translated by an IRB approved vendor and submitted to the IRB.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

See study procedures described above. No local site restrictions are planned.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

All individuals in this study will receive the current standard of care at Partners for the follow-up of abnormal cancer screening tests (Arms 1-4). In addition to this standard of care, we will test 3 additional arms of increasing intensity of intervention: Arm 2-access to an IT platform to facilitate updates to HM modifiers and problem lists for visit-based reminders; Arm 3- the IT platform in addition to automated reminders to patients (Patient Gateway messages or letters, one brief phone call or voice message) and the care team (bulk In-Basket messages); Arm 4-the IT platform, automated reminders, and administrative outreach and navigation to help with scheduling and to address social barriers to care.

Patients will only be recommended to receive care that is recommended by national guidelines/ local expert opinion. Our study is focused on ensuring that people get timely appropriate care. Since launching the study, we have found that there is a small number of patients who get care hat is not supported by national guidelines. An example of this would be a woman with a high-grade cervical abnormality who gets a repeat pap smear and not a colposcopy. In some of these instances it is documented that the patient and their personal care team had a discussion of the harms and benefits of making an alternative choice, but in others there is no documentation of why alternative care was received.

If we find that a patient has received an alternative evaluation to the diagnostic evaluation recommended by national care guidelines and there is no documentation of informed decision making, the PIs will contact the patient's PCP and/or clinical director of the primary care practice and/or the institutional ambulatory team. This will be done for patients in any of the study arms. While these patients remain eligible for our study as they will not have achieved our primary outcome, we will not contact these patients in arms 3 and 4 to minimize confusion or anxiety for the patient. Because of the small number of patients we believe that ethically this is the right choice even though it may marginally decrease our power to find an effect across the study arms.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

We will protect against risks of psychological discomfort by using neutral language in patient surveys. To prevent loss of data, all information is stored within the Partners Healthcare System, Inc. firewall, password protected, and anti-virus software enabled (or Dartmouth for Dartmouth patients). Only study staff will have access to the study data on Shared File Areas. We do not anticipate any adverse effects from this study, but we will promptly report any problem to the IRB and address any problems accordingly.

Our study is focused on ensuring that people get timely appropriate care. Since launching the study, we have found that there is a small number of patients who get care hat is not supported by national guidelines. An example of this would be a woman with a high-grade cervical abnormality who gets a repeat pap smear and not a colposcopy. In some of these instances it is documented that the patient and their personal care team had a discussion of the harms and benefits of making an alternative choice, but in others there is no documentation of why alternative care was received.

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no documentation of informed decision making, the PIs will contact the patient's PCP and/or clinical director of the primary care practice and/or the institutional ambulatory team. This will be done for patients in any of the study arms. While these patients remain eligible for our study as they will not have achieved our primary outcome, we will not contact these patients in arms 3 and 4 to minimize confusion or anxiety for the patient. Because of the small number of patients we believe that ethically this is the right choice even though it may marginally decrease our power to find an effect across the study arms.

After our study, we found that the Health Maintenance Modifiers we created were placed on 259 patients' charts by their clinicians (outside of our research). There is no functionality built in Epic to remove these modifiers when an appropriate follow-up test was received by a patient unless they were part of our study. Our study has now ended, and we have removed the health maintenance modifiers that we created. Because we didn't create the modifiers for these 259 patients, we are concerned that they will linger even if a patient has received appropriate follow-up. We will contact anyone in the Epic HMM Audit User list and ask them to review the modifier and either replace it with other functionality available in Epic or remove it. We will send 2-3 reminders over the course of 4-6 weeks. The last reminder will inform them that the modifier will be removed by our study staff.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

This protocol is minimal risk, as it is designed to improve the quality of care for patients with an abnormal cancer screening test result that is overdue for follow-up. Automated outreach (by Patient Gateway or letters) will provide information for patients to contact their PCP's office to arrange for needed follow-up. Patients in Arm 4 who are contacted by the study outreach administrator or navigator who and say that they do not want further evaluation will not be contacted further by study staff. Participants selected for the surveys will be informed that they can refuse participation at any point.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The potential risks to subjects include loss of confidentiality of healthcare data. Study staff will follow careful protocols to minimize these risks. The co-investigators will emphasize the importance of maintaining confidentiality in the training of all study staff. All study data and survey questionnaires will be coded with unique study identification numbers. Electronic data will be stored within the Partners and Dartmouth firewalls, will be password protected, and will be protected by anti-virus software. Only study staff will have access to study data on shared file areas.

Surveys may potentially cause psychological stress (topics will include barriers and facilitators to follow-up of screening abnormalities). Potential survey subjects will be informed about potential risks as part of the informational letter that they will receive before deciding whether to participate. Patients will be encouraged to discuss any concerns with their provider, prior to participating (all participants will have a PCP in this study). While unlikely, some patients may be contacted during the trial based upon inaccurate or incomplete information in her/his electronic health record. There may be psychological stress associated with such contact, but information provided by patients will be used to update the patient's record/ notify the patient's care team, thus ultimately resulting in better quality care. Study staff will specifically be trained to help patients cope with these issues. Study staff, particularly the outreach coordinators and the navigators, will be trained to specifically address any personal stressors that a patient may have that is interfering with their ability to get needed care. During the trial phase, patients are only indirectly affected through process of care modifications at the practices they attend. We do not anticipate physical risks to patients as a result of participation. Patients in the "control" arm will receive standard care as provided by their PCP and practice. Potential risks also include the time associated with survey participation for those selected. This time commitment will be minimal. Potential participants will be informed of the potential harms of participation when they decide whether to participate in a survey; participants will also be informed that they can decide to discontinue their survey participation at any time.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Participants in practices randomly assigned to the intervention arms may benefit by receiving more timely follow-up of their abnormal cancer

screening test results. Patients in control practices will receive usual care under the direction of their primary care provider. If the intervention is effective, more timely follow-up of abnormal cancer screening test results could lead to earlier detection, treatment, and cure of the cancers studied in this proposal. In the future, all patients could benefit from the knowledge produced by this study through the dissemination of similar care systems.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

We will be recruiting all individuals during the study period at the participating clinics who are eligible for screening for breast, cervical, colorectal and lung cancer screening based on current guidelines as specified above, and who receive an abnormal screening result and are overdue to receive clinically indicated diagnostic evaluation.

We only have resources to deliver this study in English and Spanish. We are aiming to recruit an ethnically and racially diverse group of patients who are representative of the eligible population.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Individuals who speak English or Spanish will be eligible, as these two languages reflect the significant majority of the Partners and Dartmouth patient populations and sufficiently allow us to meet our study goals. Once final study materials are developed in English they will be professionally translated by an IRB-approved vendor and submitted for review before they are used.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Trial: We plan to recruit 3324 participants in the RCT who fit the eligibility criteria defined above (are overdue for follow-up of an abnormal cancer screening test result). Because the trial is testing a "care enhancement" we are requesting a waiver of informed consent given the large number of subjects distributed over a maximum of 44 primary care practices. Randomization will be done at the practice level and individual patients will not be approached for recruitment. Because randomization will be done at the practice level, we will not be able to recruit exactly 3324 individuals (patients may be in process of recruitment since they will be recruited in batches) – this is the number suggested by our sample size calculation. We will not exceed recruitment of 12,000 eligible individuals. The outcomes for the main trial will be assessed using data from the electronic health records at BWH, Faulkner, MGH, NWH, NSMC, and DFCI. NWH, NSHM, and DFCI are included because patients from MGH and BWH may have tests that are performed at these sites, thus they will be included in our review for diagnostic testing. Because of the large number of study participants and the minimal risk, we request a waiver of informed consent for this portion of the trial. It would not be feasible to contact this number of individuals and as this is a pragmatic trial it would adversely affect the validity and interpretation of our results.

Surveys: Some of the outcomes of the study will be measured by PCP and patient surveys:

PCP Surveys-PCPs, excluding trainees, at participating sites using the electronic health record will be surveyed prior to launch of the RCT and 3 months after recruitment ends. Prior to fielding the survey, we will request that the primary care network director send an email to PCPs in his/ her network informing them about the purpose to the survey-will then receive an email from one of the study investigators with a link to a Redcap survey. Each PCP will receive up to 5 email contacts over 4 weeks. Remuneration is described in the appropriate section below.

PCP surveys will be sent by email via a RedCap Survey link, that will include a gift card code. The pre-trial surveys will be sent electronically during the 3 months before the trial. Post-trial surveys will be sent electronically during the 3 months following the trial. Because the trial will run for 2 years it may be different doctors who are asked to complete the survey. The consent process for the 2 surveys will be done independently because the long period of time in between.

Patient surveys: As noted above, we will randomly sample 15% of participants. Patient surveys will be administered 4-12 weeks after their individual follow-up period has been completed, so surveys will be conducted throughout the enrollment period. *Survey procedures* will include: 1) an introductory letter from the clinical director of each primary care network paired with a letter from the PI that explains the study purpose and opportunities to opt out/ participate of the survey (see attached). Patients will be given the opportunity to go to a unique Redcap url/QR code from the letter or will receive an the un-secured email. The letter will include contact directions to email/ phone study staff if they do not wish to opt-out of the survey or do not wish to receive un-secured email. Those who do not opt-out within 2 weeks will be contacted by phone and asked to complete the survey by phone or RedCap. If the patients opt for the later, they will receive the survey link via un-encrypted email (and asked for the email where they would like to receive it). Patients will receive up to 5 email/mail attempts over 4 weeks followed by up to by one phone call. All mail surveys will be sent with a pre-addressed envelope with pre-paid postage.

Remuneration is described in the appropriate section below.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subjects in the main trial will not receive remuneration.

Patients who are sampled for the survey and complete the survey will receive a $50 gift card from their choice of Amazon or a regional grocery store.

PCPs who are eligible for the survey will receive a $50 gift card code for Amazon with the initial delivery of the survey as the survey literature supports the use of "up front" incentives for health care providers.

No additional remuneration will be provided as this study does not incur any out-of-pocket expenses for participating.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects

https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects

https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

We are requesting a waiver of consent for the trial given the large number of patients and practices and the minimal risk from participation. All patients will remain under the care of their primary care team and the intervention components will be delivered in addition to those individuals who are overdue for follow-up.

The introduction to the surveys will include the elements of informed consent. As these surveys are minimal risk, we request a waiver of informed consent. Consent will be implied if the subject choses to complete the survey.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the

study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Data monitoring plan

All data collection/ storage systems will be piloted before the study begins. Any patient data collected as part of the study itself will be stored electronically on secure, Partners or Dartmouth servers behind the institutional firewall with password protection and anti-virus software. Only study staff will have access to the study data on Shared File Areas. The PIs will be responsible for monitoring and assuring the validity and integrity of the data and adherence to the IRB-approved protocol.

Safety monitoring plan

The main safety risks for the study include the potential for psychological discomfort associated with the intervention. Though this should not differ among patients in intervention or control practices, those in intervention practices may receive more timely notification of an overdue abnormal test result and information about why it is important to complete recommended follow-up. The benefits of receiving timely follow-up of an abnormal cancer screening tests substantially outweigh this risk. We will monitor complaints received from patients and/or providers and notify the local IRB as required by local governance. The main risk of the study is unintended release of patient health information collected and maintained by the study investigators. As noted, we will apply rigorous data safety and monitoring standards to ensure that this does not occur. As noted above, if we find that a patient has received an alternative evaluation to the diagnostic evaluation recommended by national care guidelines and there is no documentation of informed decision making, the PIs will contact the patient's PCP and/or clinical director of the primary care practice and/or the institutional ambulatory team. This will be done for patients in any of the study arms

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Although we do not anticipate any direct adverse events from this study, we will promptly report any such adverse events to the IRB. Currently, the Partners IRB requires that serious adverse events are to be reported to the IRB as soon as possible, within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem. Non-serious adverse events are to be reported within 20 working days.

If patients report significant complaints about our recruitment approach, study staff will document all patient concerns and provide a detailed report to the IRB about the nature of the complaint. Study staff will discuss with the PIs on how to adapt recruitment approaches to prevent future complaints, and include any changes required by the IRB.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The PIs will be responsible for monitoring and assuring the validity and integrity of the data and adherence to the IRB-approved protocol.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

To ensure patient privacy and confidentiality, all information will be stored within the Partners Healthcare or Dartmouth firewall, password protected, and anti-virus software enabled. Only study staff will have access to the study data on Shared File Areas. A limited dataset will be sent to Dartmouth using secure file transfer for data analysis. A Data Use Agreement will be in place before any data transfer occurs. Only de-identified data will be used for the purposes of publication or presentation.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

A limited dataset will be sent to Dartmouth using secure file transfer for data analysis. A Data Use Agreement will be in place before any data transfer occurs. Data elements will include a unique study ID, demographic characteristics (age, gender, race/ ethnicity, language, marital status), insurance, comorbidity, # of PCP visits in prior 12 months, # of no show visits in prior 12 months, date of abnormal cancer screening test, screening test abnormality (e.g., BIRAD 3 mammogram result), dates of any follow-up diagnostic evaluation, type of any subsequent diagnostic evaluation (e.g., subsequent mammogram, biopsy), and survey responses.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Data will be stored at Dartmouth for a period of up to 7 years from the date of the last publication that results from the data.

As noted above, Dartmouth will be a relying site on the Partners IRB using a SIRB review that will be added in an amendment once the Partners protocol is approved.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

We will receive a copy of the final limited data set from Dartmouth with pooled Partners and Dartmouth data once data collection is completed.

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mFOCUS Primary Paper Statistical Analysis Plan 5.19.2022

The goal of the primary paper is to report the primary results of the trial

1. Study cohort
    a. Primary analysis: Intent-to-treat
    - All patients who met protocol eligibility criteria for at least one abnormal cancer screen
    - Patients with multiple tests are included for only the first abnormal screen (design paper)
    - Includes patients whose ineligibility was discovered through chart review

    b. Secondary analysis: Modified Intent-to-Treat
    - All patients in the ITT analysis, but excluding those whose ineligibility was not discovered until chart review (e.g., proc cancer diagnosis; non-clinical care; language; received follow-up prior to eligibility assessment)

2. Primary efficacy outcome: Completion of follow-up within 120 days of mFOCUS eligibility (in protocol)
   Two secondary outcomes: Completion of follow-up within 240 days
   Time to completion (others in protocol, but not in this manuscript)
   Exploratory subgroup analyses: Based on the same primary and secondary outcomes above, within:
   Types of cancer (breast; cervical; CRC; lung) (in protocol)
   Severity of abnormality (low; medium; high) (in protocol)

3. Missing data: If outcomes or randomization groups are missing for more than 1% of subjects, multiple imputation will be used. If model covariates (see below) are missing for more than 5% of subjects, multiple imputation will be used.

Comments: The protocol also specified secondary outcomes based on patient and provider surveys; these will not be presented in this manuscript but will be the focus of a second publication.

In discussions (but not in the protocol), there was interest in exploring how COVID affected the outcome, in the sense that patients who became eligible when COVID was more prevalent (and elective care was less available) may have taken longer to have follow-up. Because this is a complicated topic and will distract from the main randomized results, it was decided to save such analyses for a subsequent manuscript. The current manuscript will simply adjust (through indicator variables) for 3-month time windows. Since COVID peaked in different areas at different times, these indicator variables will be included as interactions with study site (Boston versus Dartmouth).

Contents:

1. Exhibit 1: Figure 1: Consort Diagram

2. Exhibit 2: Table 1: Baseline Characteristics, by Arm
    a. Patient characteristics
        i. Sex
        ii. Age
        iii. Race/Ethnicity
        iv. Primary insurance
        v. Primary language
        vi. Marital status
        vii. Comorbidities
        viii. Number of PCP visits in prior year
        ix. Number of no show visits in prior year
        x. Type of cancer
        xi. Severity of screening abnormality
        xii. Rurality (distance or population)
        xiii.

    b. PCP characteristics (from protocol; none currently in the prototype table):
        i. Sex
        ii. Provider type (MD/ DO, NP/ PA, other)
        iii. Specialty
        iv. Panel size (not risk adjusted)

c. Clinic characteristics (from protocol; none currently in the prototype table):
    i. Location (hospital; community health center)
    ii. Visit volume at time of randomization
    iii. Patient mix (% female; % Medicaid) at time of randomization

3. Exhibit 3: Table 2: Overall Primary (120 day completion) and secondary (240 day) outcome analyses
    Intent-to-Treat and Modified Intent-to-Treat;
    "Unadjusted" and Adjusted

    a. Presentation: Data will be shown by arm, both ITT and mITT, both adjusted and "unadjusted"
        i. The overall global p-value (<0.05) for the adjusted ITT analysis will be shown. If the global test is significant, then three pairwise tests (each arm against control/Arm 1) looking for p<0.0167.
        ii. All other analyses and comparisons will be based on 95% confidence intervals

    b. Primary and secondary analyses: SAS Proc GLIMMIX with the patient as the unit of analysis and a binary outcome (completed/not completed). All models (including "unadjusted") will include random effects for practices and physicians. All models (including "unadjusted") will include fixed effects for type of cancer. All models (including "unadjusted") will include indicator variables for time (calendar month), along with interaction terms with site (Boston versus Dartmouth).

        i. Unadjusted analysis: The model above will include random effects for practices and physicians, fixed effects for cancer types, fixed effects and interactions for calendar month and study stie, and indicator variables for Arms 2, 3, and 4.

        ii. Adjusted analysis: The covariates from 2 above will be added individually to the model. Any that are significant at p<0.05 and change the coefficient of any of the 3 indicators for treatment arm by >20% will be retained in the model as confounders. (Type of cancer and calendar month will be retained in the model regardless of significance or confounding.) Adjusted completion rates will be calculated by marginal standardization and presented in the Table.

4. Exhibit 4: Figure 2: Forest plot with subgroup analyses for the primary (120 day completion) outcome
    Intent-to-Treat
    Adjusted only

a. Presentation: Data will be shown by subgroup as an odds ratio (versus the control arm 1) with 95% confidence interval; ITT; adjusted only
    i. P-values for interaction will be presented
    ii. All other comparisons will be based on 95% confidence intervals

b. Subgroup analyses: SAS Proc GLIMMIX with the patient as the unit of analysis and a binary outcome (completed/not completed). All models will include random effects for practices and physicians. All models will include fixed effects for type of cancer and calendar month.

    i. Subgroups (each set analyzed separately):
        Type of cancer (breast; cervical; CRC; lung)
        Severity of abnormality (low; medium; high)

    ii. Adjusted analysis: The model above will include random effects for practices and physicians, fixed effects for cancer types and calendar month, indicator variables for Arms 2, 3, and 4, indicator variables for the subgroups, and interaction terms for the arms-by-subgroups.
    A global test for effect modification will be run and reported. However, regardless of significance, a separate "unadjusted" model will be run for each subgroup.
    Since, some of the subgroup sample sizes will be limited, not all the covariates from the primary overall model above in (3) will be added to each stratified models. Decisions will be made based on the degree of confounding and the sample size.

c. Appendix: A similar figure will be created for the mITT data. A decision of whether to display it in the appendix will be made based on the findings.

5. Exhibit 5: Figure 3: Kaplan-Meier Curves
    a. Four curves (4 arms), unadjusted, ITT
    b. Log-rank p-value
    c. A Cox regression model will be built for the ITT data. Since only one level of clustering is available, the model will use the analogue of random effects for practices and adjust for the same variables as in the logistic regression model above.
        i. Significance testing will use a global p-value across all 4 arms and, if significant at $p<0.05$, pairwise comparisons between each arm and the control arm will be carried out. Results for the pairwise comparisons will be presented as 95% confidence intervals.
        ii. The results of the Cox regression will be reported in the text. A table of the model results may appear in the Appendix.