STUDY PROTOCOL

Title: Accelerating Colorectal Cancer Screening and Follow-Up Through Implementation Science in Chicago: UH3 Implementation Phase

Short Title: ACCSIS UH3 - Chicago

Sponsor: National Cancer Institute Moonshot Initiative

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ABSTRACT

Introduction:

Screening for colorectal cancer (CRC) not only detects the disease early but also prevents cancer by finding and removing precancerous polyps. While the percentage of the U.S. adult population that is up-to-date with recommended CRC screening increased to 65% in 2010, nearly 28% of the eligible adults have never been screened. Underuse of CRC screening is frequent among racial/ethnic minorities and low social, economic status populations. These populations disproportionately receive health care in safety-net settings, such as federally qualified health centers (FQHCs). Thus, FQHCs play a significant role in CRC prevention and control.

Objectives:

The overall goal of our project, Accelerating Colorectal Cancer Screening and Follow-Up Through Implementation Science in Chicago (ACCSIS-Chicago), is to test a multilevel, multicomponent intervention to increase rates of CRC screening, follow-up, and referral-to-care among racial/ethnic minority and low-income populations in Chicago, Illinois. The ACCSIS-Chicago is a two-phase study. During the UG3 Planning-Exploratory Phase (Year 1), we conducted in-depth interviews with one of our FQHC partners in another similar study to understand how to best increase the adoption, implementation, and sustainment of a multilevel, multicomponent intervention, and use the information to develop implementation support strategies (IRB18-1141). In the UH3 Implementation Phase (Year 2 to 5), we will implement the multilevel, multicomponent intervention in four FQHCs using a stepped wedge design and evaluate the effectiveness using multilevel modeling.

Study Design/Setting/Participants:

In the UH3 Implementation Phase, we will have 4 clusters of clinics from four different FQHCs. Each cluster will have 5 to 12 clinics and a total of 20 to 35 primary care providers (internist, family practice physician, nurse practitioners, and physician assistants). We will implement our multilevel, multicomponent intervention in three phases. In phase 1, we will implement the provider education and community outreach component to target the provider- and community-level influences. In phase 2, we will add the mobile patient reminder, and the provider assessment and feedback components to target organization-level influences. In phase 3, we will add the CRC patient navigation component to address the possible barriers that individuals face during the processes of CRC screening and follow-up.

Study Intervention and Measures:

The multilevel intervention components will include 1) provider education, 2) provider assessment and feedback, 3) patient reminder using mobile platform, 4) patient navigation, and 5) community outreach. The first three components will be implemented as part of the quality improvement project at the partner FQHCs. During the first six months, we will collect baseline data at our partner FQHCs. After we start implementing the multilevel intervention, we will collect outcome data every three months until the completion of the 4-year study period. At the clinic and provider levels, we will work with the Quality Improvement Department to collect outcome data on 1) CRC screening rates, 2) CRC screening order rates, 3) CRC screening completion rates, 4) follow-up diagnostic evaluation rates, 5) follow-up diagnostic evaluation completion rates, and 5) time to completion of diagnostic evaluation. At the patient level, we will collect data on patient navigation service utilization and the satisfaction of the services.

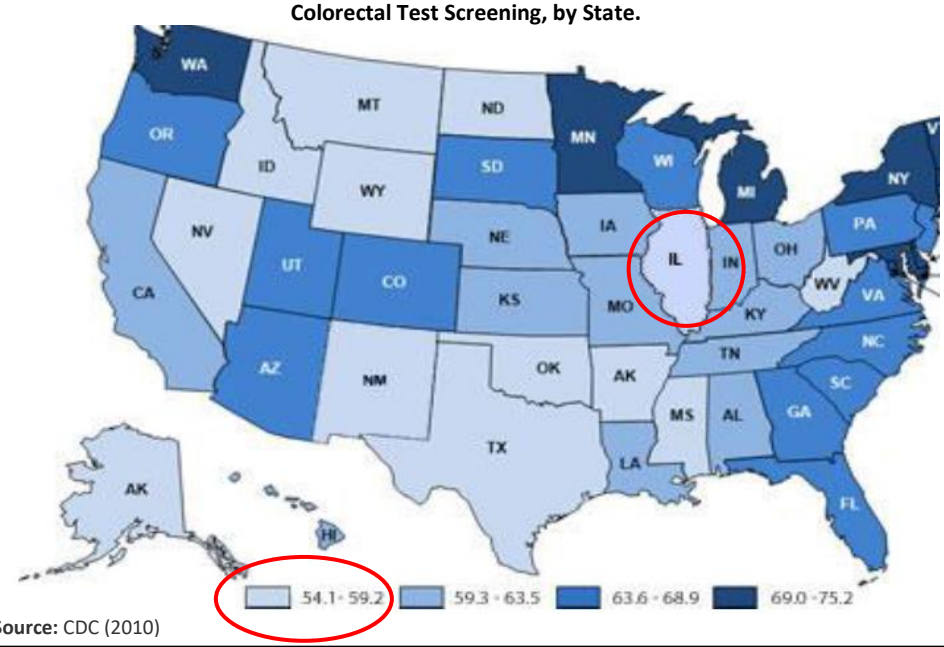
1. BACKGROUND AND SIGNIFICANCE

1.1. Background

Colorectal Cancer Burden in Illinois

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Screening for CRC not only detects the disease early when treatment is more effective but also prevents cancer by finding and removing precancerous polyps. Despite strong evidence to support CRC screening, nationally, only 65% of adults had up-to-date screening [1]. Residents in the state of Illinois are no exception, and in fact, Illinois ranks in the last quartile (54% to 50%) for CRC screening rates across the nation, as shown in *Figure 1* [2]. This disturbing statistic has no doubt been a contributor to the high CRC incidence in Illinois. In 2013, Illinois had the 13th highest age-adjusted CRC incidence rate in the nation at 42.9/100,000 [2]. Among communities of color, African American (AA) males and females in Illinois rank the 8th highest CRC mortality rate in the nation [3]. Furthermore, Illinois has the 5th largest number of Hispanic and Asian-American populations in the nation. Both Hispanic and Asian Americans have significantly lower CRC screening rates compared to Non-Hispanic White and Black [4].

Figure 1: Percentage of Adults Aged 50–75 Years Who Reported Being Up-to-Date* with Colorectal Test Screening, by State.



Source: CDC (2010)

Colorectal Cancer Burden in Cook County

Cook County is the most populous county in Illinois and the second-most populous county in the United States. According to the 2010 census, Cook County had 5,194,675 residents, who represented 40% of all residents in the state of Illinois. Furthermore, 24% of Cook County residents (or 1,253,354 individuals) were between the ages of 50 and 74 years in 2010 [5]. Although Cook County has a similar CRC incident rate as Illinois, its CRC mortality rate is significantly higher than the Illinois overall rate and ranks 3rd across the 102 counties in Illinois [5]. Some of Cook County's

Table 1: Population Estimates of Designated Regions in Illinois

	Illinois	Cook County	Chicago
Population*	12,875,255	5,231,351	2,695,598
NH White**	77.9%	65.9%	45.0%
NH Black**	14.8%	24.6%	32.9%
Hispanic**	16.3%	24.6%	28.9%
Asian***	4.7%	6.4%	5.5%
% Living below 200% of the poverty level	30.8%	35.2%	43%

* 2012 Population estimates from the U.S. Census Bureau.
** Race data may be above or below 100% due to estimate methodology that includes multi-racial individuals in each racial group.
*** 2009-2013 American Community Survey 5-Year Estimates.

population characteristics may contribute to the colorectal cancer burden. Compared to other counties in Illinois, Cook County has the most diverse population with significantly higher numbers of African Americans, Hispanics, Asian Americans, as well as people who are living below 200% of the poverty level (*Table 1*) [5]. Studies have consistently shown that racial and ethnic minorities, as well as those living in poverty, suffer disproportionately from health disparities, and the 2010 National Health Interview Survey (NHIS) found that CRC screening rates were significantly lower among racial/ethnic minorities compared to whites (59.8%), Blacks (55.0%), Hispanics (46.5%) and Asians (46.9%) [6]. The low socioeconomic indicators and poor CRC health outcomes experienced by a disproportionate number of Cook County residents underscore the critical need to create a more organized approach to CRC prevention and control in the county. Cook County is also home to the City of Chicago, where approximately 54% of county residents reside. Chicago is the 3rd most populous city in the U.S., and its CRC mortality rate overall is 21.5 deaths per 100,000, higher than the nation's overall colorectal cancer mortality rate of 17.5 deaths per 100,000. Chicago also has the 2nd largest African American population, 4th largest Hispanic population, and 5th largest Asian American population in the nation. Although efforts have been in place to improve CRC outcomes in Chicago and Cook County, the lack of coordination across different sectors and attention to multilevel influences diminish the impact of such efforts.

Safety-Net Health Care Systems and Colorectal Cancer Control

Although the percentage of the U.S. adult population that is up-to-date with recommended CRC screening increased from 54% in 2002 to 65% in 2010 [7], nearly 28% of the eligible adults still had never been screened [2]. Individuals who were without health insurance and a regular care provider were more likely to have never been screened than those with health insurance and with a regular care provider [2]. Racial/ethnic minorities and low social, economic status (SES) populations are among those who lack health insurance and a usual source of care. Underuse of CRC screening is frequent among these populations [8-10], who disproportionately receive health care in safety-net settings, such as federally qualified health centers (FQHCs) [7, 11]. FQHCs are designed to provide comprehensive, quality primary health care services to medically underserved communities and vulnerable populations. In 2016, FQHCs served 26 million patients, of whom 23% were uninsured, 62% were racial/ethnic minorities, and 92% were living below 200% poverty level [12]. Because many of our nation's most disadvantaged and vulnerable individuals make use of FQHCs to obtain health care, FQHCs play a significant role in CRC prevention and control.

1.2. Significance

The overall goal of our project, ***Accelerating Colorectal Cancer Screening and Follow-up through Implementation Science in Chicago*** (**ACCSIS-Chicago**), is two-fold: 1) to understand how to best increase the adoption, implementation, and sustainment of evidence-based interventions; and 2) to provide the evidence base for multilevel interventions that increase rates of CRC screening, follow-up, and referral-to-care among racial/ethnic minority and low SES populations. The ACCSIS-Chicago will focus on Cook County geographically, especially in Chicago, where 54% of the Cook County population resides. We will partner with local FQHCs, community-based organizations, and workplaces to increase rates of CRC screening, follow-up, and referral-to-care among racial/ethnic minority and low SES populations. The ACCSIS-Chicago project will use two types of implementation strategies to increase rates of CRC screening, follow-up, and referral-to-care among racial/ethnic minority and low SES populations: 1) a multilevel intervention, which will have multiple components, and 2) implementation support strategies to accelerate the adoption, implementation, and sustainment of the multilevel intervention. In the UH3 Implementation Phase, we will partner with 4 FQHCs, which have 35 clinics in the Chicago area and provide primary care service to racial/ethnic

minority and low SES populations. Together, these 4 FQHCs served more than 188,037 patients in 2016. We will use a stepped wedge cluster randomized trial design to examine the effectiveness and impact of our multilevel interventions on increasing rates of CRC screening, follow-up, and referral-to-care across these 4 partner FQHCs. We will also implement a local innovation, ILColonCARES Program, and assess its feasibility and effectiveness on the follow-up of a positive FIT.

2. STUDY OBJECTIVES, DURATION, AND STUDY SITES

2.1. Study Objectives

Objective 1: *Collect baseline data during the first 6 months before implementing any intervention component.*

Objective 2: *Implement the intervention in three phases: 1) provider education plus community outreach; 2) add provider assessment and feedback + patient reminder; and 3) add a CRC navigator program.*

Objective 3: *Create a grand model to test the overall effectiveness of the multilevel intervention on primary outcomes within and across levels, as well as separate models to access effectiveness at each phase.*

Objective 4: *Identify potential interaction or mediation effects and assess such effects on primary outcomes.*

Exploratory Objective 5: *Implement a local innovation, IL ColonCARES Program, and assess its feasibility and effectiveness on the follow-up of abnormality.*

2.2. Study Duration and Study Sites

The ACCSIS – Chicago UH3 Implementation Phase will last for four years (November 2019 to October 2023). In the UH3 Implementation Phase, we will have 4 clusters of clinics from four different FQHCs. Each cluster will have 5 to 12 clinics and a total of 20 to 35 primary care providers (internist, family practice physician, nurse practitioners, and physician assistants). Table 1 summarizes the characteristics of our FQHC partners. Together, our

Table 1: Characteristic of Partner Health Care Systems

	Total Patients	% of Racial Minority	% at or below 200% poverty	% of Uninsured	CRC Screening Rate	Adjusted Quartile Ranking on CRC Screening[1]	No. of Clinics[2]	No. of Providers
PCC Community Wellness Center	48,357	92.2%	93.1%	9.3%	30.0%	Quartile 4	11	60
Aunt Martha's Youth Service Center, Inc.	51,343	80.9%	96.2%	16.5%	32.9%	Quartile 3	12	21
Lawndale Christian Health Center	51,235	96.9%	97.6%	30.2%	35.0%	Quartile 2	5	35
Near North Health Service Corporation	37,102	94.6%	97.3%	35.1%	31.0%	Quartile 3	7	20

1. Adjusted Quartile Ranking provides a health center's adjusted quartile ranking compared to health centers nationally for each of the clinical performance measures. Clinical performance for each measure is ranked from quartile 1 (highest 25% of reporting health center) to quartile 4 (lowest 25% of reporting health centers).
2. Reported by partner health care system.

partner FQHCs served 188,037 patients in 2016, and at least 10% of these patients were ≥ 50 years old. It is important to point out that three of our partners' CRC screening rates were in the lower third and fourth quartiles compared to other FQHCs in the nation, indicating room for improvement. We will continue to monitor their ranking throughout the study.

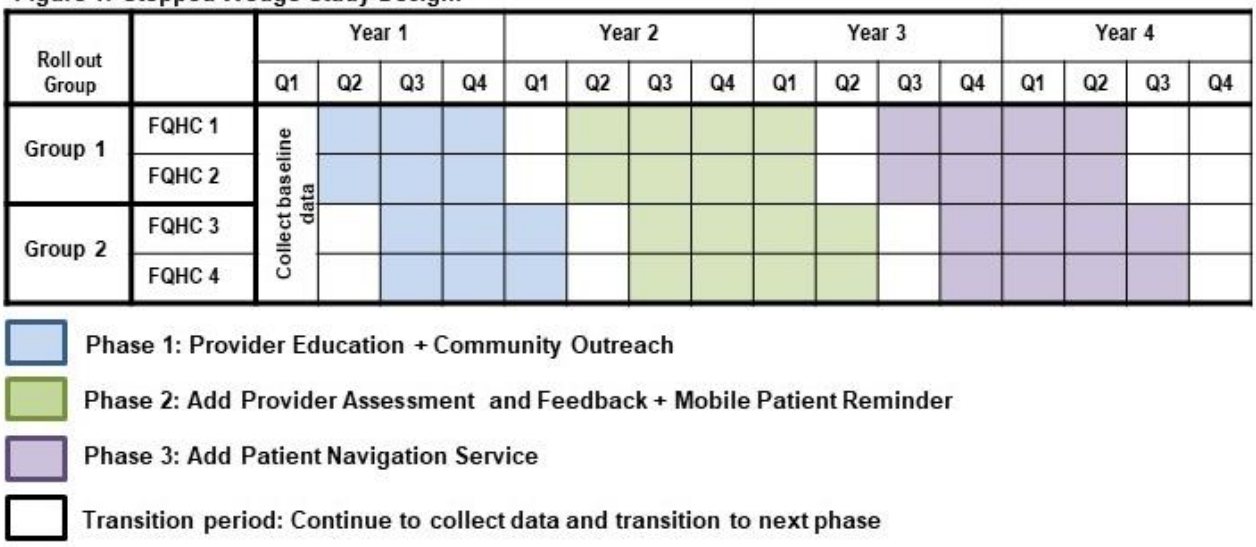
3. STUDY DESIGN AND PROCEDURES

3.1 Study Design

We will use a stepped wedge cluster randomized trial design to assess the effectiveness of our proposed multilevel intervention. Although it will be preferable to use a traditional cluster-randomized trial to test our multicomponent, multilevel intervention, we will need a larger number of clusters, which will be more expensive and infeasible. Also, it is unacceptable for our partner(s) assigned to a control group to not benefit from well-studied evidence-based interventions. Since the stepped wedge design retains some elements of randomization and has the advantage for multiple data collection points over a long period and allows clusters to act as their own control, it is the best alternative to the gold standard.

In the UH3 Implementation phase, we will partner with four FQHCs. We will randomize the four FQHCs to either group 1 or group 2. The biostatistician will conduct the randomization independently from the research team. The difference between the two groups is that group 2 will start the implementation later. We will implement our multilevel intervention in three phases. In phase 1, we will implement the provider education and community outreach component. In phase 2, we will add the mobile patient reminder and the provider assessment and feedback components. In phase 3, we will add the CRC patient navigation component. Figure 1 shows our stepped wedge study design.

Figure 1: Stepped Wedge Study Design.



3.2 Study Intervention

CRC screening and follow-up processes are complex and include several steps and interfaces. However, very few interventional studies have simultaneously targeted patient-, provider-, and organization-level factors. At the patient-level, factors influencing motivation and willingness to undergo CRC screening or diagnostic evaluation after a positive result may include negative beliefs or attitudes about cancer screening, lack of health insurance coverage, suboptimal knowledge about the necessity of screening and/or follow-up diagnostic evaluation, and other SES barriers [13-20]. At the provider-level, factors include overburden [21],

communication issues [22], lack of a place for referrals [23], and decisions made by the provider not to screen or follow-up [24]. At the organization-level, factors include interruption or breakdowns in the workflow, nonadherence to organizational policy, and lack of "intra-organizational" and "inter-organizational" coordination [25]. Interventions that simultaneously focus on reducing barriers across several levels will likely be more effective on increasing rates of CRC screening, follow-up, and referral-to-care. In this study, we will partner with the Quality Improvement Department at each partner FQHC to implement provider education, provider assessment and feedback, and mobile patient reminder as part of the organizational CRC Screening Quality Improvement Initiative.

3.2.1 Provider-Level Component:

Provider Education CRC screening, follow-up and surveillance guidelines, cultural competency and communication training for primary care providers is a must if we are to increase CRC screening and follow-up adherence and decrease cancer disparities among racial/ethnic and low-income populations, as well as in the general population. Drs. Kim and Polite are well-known CRC control experts and will identify critical messages on CRC screening guidelines and options, and provide in-person educational training to providers in our partner FQHCs. In addition, they will conduct refresher sessions and yearly training. Dr. Kim and Dr. Polite will also train a healthcare member of the ACCSIS-Chicago team to serve as a practice facilitator, who will have a medical background and understands the clinical practice, to provide one-on-one training for new providers and providers whose CRC screening rates fall below the benchmark on two consecutive provider assessment and feedback reports. The facilitating sessions for providers whose CRC screening rates below the benchmark will be limited to 10-15 minutes to refresh key messages on CRC screening and to identify possible barriers. In our experience, underperformers were often the result of failure to adequately document FIT results into the EMR system rather than an unwillingness to screen patients. Tracking these potential barriers can significantly improve screening rates.

Provider Assessment and Feedback Provider assessment and feedback is designed to both evaluate provider performance in recommending and offering screenings to age-eligible patients (assessment) and present providers with information about their performance in providing CRC screening services (feedback). We will work with the quality improvement team at our partner sites to generate clinic- and provider-specific reports on CRC screening completion rate, referral rate, as well as follow-up for abnormal results and referral to oncology care. Also, we will monitor group performance (e.g., the mean performance for a specific site or group). Providers will receive a quarterly report that allows providers to compare their performance to that of their peers and to learn from each other's successes. Our research team will deliver the reports in person for the first two quarters to provide support and open discussion to address any concerns about the process and the interpretation of the results. Education and training will be provided to reinforce compliance when a partner site's group or individual performance is at or below baseline on two consecutive reports.

3.2.2 Organization-level Component

Patient Text Message Reminder Completion of screening and follow-up evaluation involves patient compliance with the provider recommendation. It is critical not only to remind providers to order the screening test but also remind patients to complete the test. We will work with our partner sites to implement a mobile patient reminder as part of the quality improvement initiative. The patient reminder app combines technologies in mobile communication and artificial intelligence to engage patients and deliver customized messages and timely information to empower patients to complete their screening. Text message reminder has been reported to have a positive impact on patient compliance. [25-26]

CRC Patient Navigation Completion of screening and follow-up evaluation involves patient compliance with the provider recommendation. Therefore, we will add a CRC navigator to facilitate patient compliance at both organization and patient levels. Patient navigation is a healthcare delivery support strategy and was first introduced by Harold P/ Freeman in 1990 as a way to reduce cancer disparities by eliminating barriers to timely care between the point of suspicious finding and the resolution of the finding by diagnosis and treatment [27]. Most patient navigation programs have been created to improve rates of CRC screening [28-36], and few studies have used patient navigators to improve outcomes related to diagnostic follow-up after a positive test result [37-41].

Our partner FQHCs will hire a patient navigator for their CRC Patient Navigation Program with support from the research team. All hired patient navigators will participate in a 2-day training session. Our patient navigator training includes didactic and clinical training sessions, as well as CITI human subject training. Training will take place 3 months before the implementation of the component with ongoing training every quarter through the duration of the program. Drs. Kim and Polite and the research team will lead the training. The training will focus on, but not limited to, the following topics: CRC and CRC screening methods, the follow-up process after a positive FOBT/FIT, cancer treatment, navigator roles and responsibilities, common patient barriers, communication skills with health care providers and other professionals, cultural competency, local community resources, and the oral consent process and the participant's right. Furthermore, the CRC navigators will have the opportunity to spend time in the University of Chicago endoscopy suite with Dr. Kim and the oncology clinic with Dr. Polite observing colonoscopies and patient-provider interactions. The goal of these activities is to create an interactive environment that allows navigators to gain knowledge through direct experience. CRC navigators will undergo pre and post-training evaluation to assess their knowledge for CRC screening and follow-up care. All CRC navigators will meet with a research team member biweekly to discuss their cases, share information, and address any issues associated with their roles and responsibilities.

ILColonCARES Program Many safety net settings with low resources offer FOBT/FIT as the initial screening option for their patients [42, 43]. However, providers in these settings often face an ethical dilemma: whether to offer no screening or to offer the screening knowing that the patient with a positive FOBT/FIT result cannot obtain timely follow-up colonoscopy services. In Chicago, the lack of specialty services for colonoscopy access within our safety net system is a significant problem with the average wait of 18 months to complete a diagnostic colonoscopy. This alone can significantly contribute to disparities in colorectal cancer mortality with studies showing that a one year delay in follow up for a positive FIT can result in a twofold increase in colorectal cancer risk [44]. Thus, it is important to increase the ability of safety net providers to access high quality and timely colonoscopies for their underinsured or uninsured patients when a follow-up is needed. ILColonCARES Program is a HIPAA compliant web-based portal designed and developed using a user experience approach to link non-networked healthcare systems. Some hospital health systems in Chicago have committed to providing no-cost colonoscopy services to uninsured FIT positive individuals. The ILColonCARES Program overcomes many barriers to receipt of colonoscopy services across systems: 1) access to care for uninsured patients, 2) point of service scheduling, 3) bidirectional communication. The ILColonCARES Portal was created by a CDC funded program and is housed in the University of Chicago. Our partner FQHCs will have access to the portal.

3.2.3 Community-Level Component

Community Outreach Reliance solely on primary-care settings to promote and provide colorectal cancer screenings can only reach those who have regular contact with the health-care system. In ACCSIS-Chicago, we will partner with the National Outreach Network program at the University of Chicago Comprehensive Cancer Center to conduct community outreach activities. We will expand the current community outreach networks and will build new partnerships with high-risk communities located near our partner FQHCs. We will continue the NCI's Screen to Save (S2S) Initiative through small media campaigns in the high-risk communities and conduct community education events. For participants without a regular place for care, we will work with our partner FQHCs to develop a referral channel for them to obtain CRC screening.

3.3 Recruitment For Patient Navigation

We will have recruitment posters and flyers in each exam room and patient waiting area at our partner sites. Patients who have a CRC screening order and need help to complete the screening, such as making an appointment for the colonoscopy at a local hospital or instruction on the preparation for the colonoscopy, can call the patient navigator at each partner site directly. Patient navigators help patients with any challenges that may inhibit screening completion by discussing the process through a series of up to 4 phone calls. Participation in the patient navigation program is voluntary.

3.4 Inclusion And Exclusion Criteria

The inclusion criteria for the patient navigation component include 1) having an order for CRC screening, and 2) capable of giving consent. We will not exclude any participants who meet the inclusion criteria based on age, gender, language, or racial or ethnic group.

3.5 Data Sources

During the first three months, we will work with the Quality Improvement Department at each partner site to collect baseline data on primary outcomes through the existing electronic medical record or chart reviews. After we start implementing the multilevel intervention, we will collect primary outcome data each quarter until the completion of the 4-year study period. Table 2 summarizes the primary outcome measures.

Table 2. Outcome Measures for the Multilevel Intervention

Outcome	Operational Definition	Data Sources	Data Collection Period	Level of Data Analysis
Patient CRC screening rates	Numerator: # of patients completed CRC screening Denominator: # of patients eligible for CRC screening	• EMR • Chart reviews as needed	Every quarter	Level 2, Level 3, Level 4
CRC ordering rates	Numerator: # of patients received order for CRC screening Denominator: # of patient eligible for CRC screening	• EMR • Chart reviews as needed	Every quarter	Level 2, Level 3, Level 4
Patient notification rates (FOBT/FIT +)	Numerator: # of patients notified Denominator: # of patients had FOBT/FIT +	• EMR • Chart review as needed	Every quarter	Level 2, Level 3, Level 4
Time to notification of positive results	# of days between notifying a patient with a positive result and the result available to the provider	• EMR • Chart reviews as needed	Every quarter	Level 2, Level 3, Level 4
Follow-up diagnostic evaluation referral rates	Numerator: # of patients received referral for evaluation Denominator: # of patients had FOBT/FIT +	• EMR • Chart reviews as needed	Every quarter	Level 2, Level 3, Level 4
Time to referral for follow-up diagnostic evaluation	# of days between the referral and the result available to the provider	• EMR • Chart reviews as needed	Every quarter	Level 2, Level 3, Level 4
Follow-up diagnostic evaluation completion rates	Numerator: # of patients completed diagnostic evaluation as ordered Denominator: # of diagnostic evaluation referral made	• EMR • Chart reviews as needed	Every quarter	Level 2, Level 3, Level 4
Time to completed diagnostic evaluation	# of days between the positive FOBT/FIT result available to the provider and the completion of the diagnostic evaluation	• EMR • Chart reviews as needed	Every quarter	Level 2, Level 3, Level 4

* Level 2 = Provider level; Level 3 = Clinic level; and Level 4 = organization level.

For the CRC navigation component, we will collect data from the navigator activity logs, including the number of patients using the service, length of the encounter, types of encounter (e.g., transportation arrangement or making an appointment), and types of action taken. We will also ask patients who received navigation services to complete a 10-item patient satisfaction survey adapted from the patient satisfaction survey developed by the NCI-sponsored Patient Navigation Research Program, which has been validated through rigorous structural and reliability analysis [45]. For the community outreach, we will collect annual data on the number of education events conducted and the number of community members educated.

4. DATA ANALYSES

In order to evaluate the effect of the multilevel, multicomponent intervention, we will take a step-by-step approach. First, each intervention effect at each time phase will be estimated separately using linear-mixed effects models. The estimate of intervention effect in each model will be used to test if additional intervention component significantly affects outcome measures. Next, we will develop a grand model including all three intervention effects simultaneously in addition to the models described above.

In this study, patients are nested within providers and providers are nested within clinics. The problem with nested data structures is that they violate the independence assumption of traditional regression models. Thus, we will use multilevel modeling to analyze our data. We will start with the unconditional three-level random intercept models:

Level – 1: $Y_{ijk} = \beta_{0jk} + e_{ijk}$;

Level – 2: $Y_{ijk} = \beta_{0k} + u_{jk} + e_{ijk}$

Level – 3: $Y_{ijk} = \beta_0 + v_k + u_{jk} + e_{ijk}$

where Y_{ijk} is the observed outcome for patient i with provider j in clinic k. β_0 is the mean response across all clinic. v_k is the random effect of clinic k, u_{jk} is the random effect of provider j, and e_{ijk} is the residual error. The random effects and residual errors are assumed independent of one another.

Adding predictor variables to the models is straightforward. For example, the level-3 random intercept and slope model with one predictor measured at each level is $Y_{ijk} = \beta_0 + \beta_1 X_{1ijk} + \beta_2 X_{2jk} + \beta_{3k} + v_k + u_{jk} + e_{ijk,}$ where $\beta_0 + \beta_1 X_{1ijk} + \beta_2 X_{2jk} + \beta_{3k}$ is the fixed effect of the model and $v_k + u_{jk} + e_{ijk}$ is the random effect of the model. The fixed effect of the model specifies the overall mean relationship between the response and the predictor variables. The random effect of the model specifies how the provider and clinic specific relationships differ from the overall mean relationship. To assess the potential mediator effect, we will use the causal variable and the mediator variable as predictors in the model. To assess the cross-level interaction effects, we will add a product term to the model. For example, the model for a level-1 predictor (e.g. age) cross-level and interact with a level-2 predictor: $Y_{ijk} = \beta_0 + \beta_1 X_{1ijk} + \beta_2 X_{2jk} + \beta_3 (X_{1ijk} \bullet X_{2jk}) + u_{0jk} + u_{1jk} X_{1ijk} + e_{ijk.}$ Since one of the patient-level (level-1) outcome measures is dichotomous (whether the patient adherence to follow-up diagnostic evaluation after a positive result within 9 months or not), we will add another level-1 model for the binary data:

Level – 1: $\log [P_{ijk/} (1 - P_{ijk})] = \beta_{0jk} + \beta_1 X_{ijk}$.

In this study, we will use the restricted maximum likelihood (**REML**) to estimate variances. REML treats the regression coefficients as unknown quantities to be estimated based on sample data and subtracts the needed degree of freedom when computing variance estimates. Since REML only allows for tests of models that differ in their variances, we will calculate the intraclass correlation (**ICC**) to access the variation in response variable across providers and across clinics prior to testing the models. At the end of the analysis, we will use the likelihood ratio test to

compare the nested models. The deviance values (-2 *log Likelihood*) for the two models can be used to decide which model better fits the data:

$$(-2log\ L_{\text{Reduced Model}}) - (-2log\ L_{\text{Full Model}}) = \text{deviance}_{\text{Reduced Model}} - \text{deviance}_{\text{Full Model}}$$

Statistical analyses will be conducted using Statistical Package for the Social Science (SPSS) version 23.0 and the significant level will set at alpha ≤ 0.05.

5. STUDY MANAGEMENT

5.1 Data Management

During data extraction from EMR, the medical record numbers will be converted to unique study numbers. Data files used for statistical analyses will have only unique study numbers and will not contain the 18 HIPAA personal health information identifiers. We will work with the University of Chicago Center for Research Informatics' bioinformatics and clinical trial management core to manage our data, and all data will be entered into RedCAP (Research Electronic Data Capture) at the University of Chicago. REDCap is a clinical data warehouse. The data storages at REDCap are secure, encrypted, and compliant with HIPAA.

5.2 Confidentiality

All information collected from study participants and medical records during the project period will be kept confidential, including information collected and stored in written and electronic form. Besides safeguards for confidentiality described under Data Management (Section 5.1), we will take additional steps:

1 Any paper copies of identifying information and other study materials will be maintained in locked file cabinets in locked offices.
2 Electronic data files will be secured via server maintenance that includes password protection, limited access to data by staff, different levels of access depending on the person's specific position on the team, and server securities.

5.3 Regulatory and Ethical Considerations

5.3.1 Risk Assessment

Participation in this study (patient navigation component) has minimal risk. Participants may feel discomfort answering the survey questions as they include some sensitive questions, such as "my navigator makes me feel comfortable." Participants can choose not to answer the question or stop participating in the study at any time without any risks. There are no known physical, financial, or legal risks associated with the satisfaction survey. Another potential risk to our participants is the possibility of breaches of confidentiality.

5.3.2 Potential Benefits

Patients participate in the patient navigation program may find the patient navigation service helpful to complete their colorectal cancer screening. In addition, their response to the patient satisfaction survey may help us improve patient navigation services.

For the societal benefit, there is a pressing need to reduce disparities in CRC outcomes, especially among racial/ethnic minority populations and among populations who live in poverty. Single level interventions are often insufficient to lead to sustained changes in CRC screening, follow-up, and referral-to-care. Multilevel interventions with multiple components will affect not only the desired outcomes but also each other that may add additional impacts.

6. REFERENCES

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