424 R&R and PHS-398 Specific
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PI: **Miller, David P**	Title: A Primary Care Multilevel mHealth Colorectal Cancer Screening (mCRC) Intervention	
	FOA: PA11-260	
	FOA Title: RESEARCH PROJECT GRANT (PARENT R01)	
1 R01 CA178941-01		
	Organization: WAKE FOREST UNIVERSITY HEALTH SCIENCES	
	Department: Int Med-General	

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☒ Yes ☐ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☒ No

2. * Are Vertebrate Animals Used? ☐ Yes ☒ No

2.a. If YES to Vertebrate Animals

3. * Is proprietary/privileged information included in the application? ☐ Yes ☒ No

4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No

5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

Project Summary

Colorectal cancer (CRC) screening saves lives yet remains underutilized in the United States, with approximately 1 in 3 eligible Americans remaining unscreened. Prior research has documented numerous barriers to CRC screening, including patient factors (i.e., lack of awareness of screening options, negative attitudes and beliefs, low health literacy) and provider/system factors (i.e., lack of physician time, scheduling barriers, absence of after-visit patient support). Prior attempts to increase CRC screening have generally targeted either patient or provider/system barriers, with only modest results. To achieve the highest screening rates possible, a multilevel intervention that is time-efficient, easily implemented, and appropriate for varying literacy levels is urgently needed. The increasing popularity of user-friendly mobile devices makes mHealth, or the use of mobile technology to enhance patient care, an attractive option. We have designed an innovative low cost intervention to increase the receipt of CRC screening by leveraging mobile technology to inform, activate, and support patients before, during, and after their primary care visits. Our intervention can be easily disseminated and implemented in primary care practices and is appropriate for patients of all literacy levels. This project will evaluate the efficacy of our innovative multilevel mHealth CRC screening intervention (mCRC). The conceptual framework for the mCRC system is based on the social cognitive model emphasizing reciprocal determinism, or the dynamic interaction of the person, the behavior, and the environment. The mCRC system includes: 1) a tablet CRC screening decision aid that will collect patient information, deliver a screening message, and allow patients to make a screening decision; 2) “self-service” protocols that empower staff to order patient-requested screening tests; and 3) post-decision follow-up support for patients via automated and interactive text messaging. We will test the mCRC system in a randomized controlled trial conducted in community-based primary care practices serving a racially and socioeconomically diverse population. Patients will be randomized to either the mCRC system or a tablet educational program about healthy lifestyle habits. The trial will evaluate: 1) the ability of the mCRC system to increase receipt of CRC screening within 24 weeks as confirmed by medical chart reviews; 2) the potential mechanisms of change by which the mCRC system facilitates screening (i.e., patient ability to form a screening decision, patient attitudes and beliefs, patient self-efficacy, patient intention, and the occurrence of patient-provider CRC screening discussions); and 3) the additional cost of the mCRC system per patient screened, focusing on the system costs of staff time and technology. At the completion of our study, we will make the mCRC system freely available to help increase CRC screening and improve public health.

Project Narrative

Even though colorectal cancer (CRC) screening is widely recommended and decreases mortality, almost one-third of Americans fail to get screened. To increase CRC screening in primary care practices, we will test an innovative system that includes an iPad patient education program, "self-service" ordering of CRC screening tests, and an automated interactive text messaging program to support patients throughout the screening process. Our study will help primary care practices increase and improve CRC screening for their patients, ultimately saving lives.

FACILITIES AND OTHER RESOURCES

Institutional Environment

The study proposed in the current application will take place at Wake Forest Baptist Medical Center (WFBMC). WFBMC is comprised of Wake Forest School of Medicine (WFSM, the academic entity) and Wake Forest Baptist Health (WFBH, the clinical enterprise, including North Carolina Baptist Hospital and affiliated outpatient clinics). The Medical Center's catchment area is unique, drawing a substantial proportion of its clinical population from a 24-county region, particularly in western North Carolina and southwestern Virginia. The hospital is the largest tertiary care center for the Piedmont region of the Southeast. *US News and World Report* ranks WFBMC among the top 50 hospitals in the U.S. for geriatrics, neurology/neurosurgery, urology, gastroenterology, nephrology, pulmonology, and cancer care. WFBMC is ranked as the 2nd hospital in the state of North Carolina.

The active research program at WFSM is reflected in the establishment of 13 Research Centers, which focus on the following research areas: aging, brain tumors, **cancer**, cancer genomics, complementary and alternative medicine, diabetes, human genomics, hypertension and vascular disease, imaging, **minority health and health disparities**, **medical teaching and education**, workers' health, and women's health. There are three institutes, one in regenerative medicine, one in pediatric trauma, and one in **translational science**. Center and Institute Directors report directly to the Dean. WFSM received nearly $213.3 million in total costs for research from extramural grants in FY 2010-2011, of which 94% was federally funded. This ongoing success is a direct result of an active program by the administration to support, and for the faculty to embrace, new technologies and research opportunities as they emerge. The Medical School's successful and continually evolving research programs provide a strong and dynamic setting. The Division of Public Health Sciences brought in $35.8 million among its 3 constituent departments. Internal Medicine ($28.5 million) was also a top department.

Institutional resources pertinent to the current application are described below.

Office of Research: The Office of Research is under the purview of the Dean of the School of Medicine (Edward Abraham, MD) and provides services related to research administration for all WFSM faculty. Preaward grant and contract administration includes: advice and guidance, identifying funding sources, institutional review and clearance of applications, and assistance with agency site visits. The Research Support Core provides preaward grant editing, advice on funding sources and resubmissions, and statistical assistance to WFSM faculty. Postaward grant and contract administration includes: advice and guidance, policy interpretation, agency liaison, and rebudgeting actions. The office also provides management and support of institutional committees: the Institutional Review Board, the Animal Care and Use Committee, the Intramural Research Support Committee, the University Patent Committee, and the Biosafety Committee.

The Coy C. Carpenter Library contains nearly 30,000 books, over 129,000 serials, and over 3,000 periodicals and serials subscriptions (including electronic subscriptions) in over 32,000 sq. ft. All catalog items are accessible via a computer-based catalog system.

The NIH-supported Comprehensive Cancer Center of Wake Forest University (CCCWFU) has been the driving force in the rapid and sustained growth of cancer programs within the institution and region, as highlighted below:

1. All NCI-funded faculty members at Wake Forest University as well as all cancer-focused researchers and clinical faculty are active members of the CCCWFU. This longstanding tradition has allowed the Center and its Director to speak with a single voice regarding cancer programs to the Medical Center Administration and our larger Piedmont community. **David Miller, MD, MS** (PI) and **Kate Weaver, PhD, MPH** (Co-I) are members of the CCCWFU and as such have access to the Caner Center's resources.
2. The CCCWFU drives interaction across departments at our Medical Center. Cancer Center meetings, pilot grants, and invited speakers are the major interdepartmental activity of those engaged in basic, clinical and population cancer research. This has been true for 20+ years, but is particularly critical in this time when increased demands on clinicians and researchers have forced faculty nationwide to limit scholarly interaction. Some examples: the CCCWFU grand rounds is a shared activity of Hematology-Oncology, Radiation Oncology, and Surgical Oncology; the CCCWFU program meetings of the basic

scientists occur weekly, and are among the best attended seminars at the institution. Noontime education seminars sponsored by the Cancer Center in clinical cancer topics are required meetings for Radiation Oncology residents, Hematology-Oncology fellows, and Ph.D. students in the Department of Cancer Biology.

3. The CCCWFU is the model of interaction our medical center uses to craft other interdepartmental activities.
4. The leaders of cancer research in the medical center - clinical, population-based, and laboratory - are the leaders of the Cancer Center. Programs include Cancer Control, Clinical Research, Cell Growth and Survival, DNA Damage and Cellular Defense; the Breast Center of Excellence, the Prostate Center of Excellence, and the Brain Tumor Center of Excellence; and an Initiative on Complementary and Alternative Medicine.
5. The CCCWFU has had a number of unique areas of emphasis that have distinguished it from many other Cancer Centers: 1) It has a longstanding record of success with programs targeted to African American and Native American minorities. For example, in the last 5 years of our Research Base grant, 17% of patients accrued in cancer control trials were minorities, equivalent to the rate of new cases diagnosed within those populations. 2) It has accrued patients to clinical trials, both investigator-initiated at our Center and to national cooperative groups, at rates that are particularly impressive considering our institutional size. 3) It has effectively used the entire 5-state Piedmont population as a "laboratory" setting, reaching beyond the confines of the medical center walls to serve our regional population and ask population-based questions, particularly in relation to the barriers to access to cancer care. 4) The Cancer Center has a long tradition of establishing mechanisms to foster clinical trials in the institution and region, including the Center's Piedmont Oncology Association (POA) and the long and close working relationship with the Southeast Cancer Control Consortium (SCCC) Community Clinical Oncology Program (CCOP). These now fall within the umbrella of the NCI-supported Research Base Grant, which allows 11 CCOPs in 15 states to identify our Cancer Center as a "research base", gaining CCOP credits for accrual to our institutional trials. This attests both to the quality of our research questions in these areas and our ability to organize an infrastructure to make the trials readily available to community oncologists.
6. The Cancer Center is served by the Psychosocial Oncology Program (POP) and the Cancer Patient Support Program (CPSP) that provide individual counseling to patients and/or family members (inpatient and outpatient), support groups, and educational/informational resources. The CCCWFU administrative structure allows for the development of protocols that accompany chemotherapy protocols as well as protocols focused primarily on QOL and/or psychosocial interventions. The POP and CPSP are closely linked to various departments in the Medical Center including Surgical Oncology, Radiation Oncology, Medical Oncology and Gynecologic Oncology, which provides a strong framework for collaborative research. Shared research resources of the CCCWFU, in addition to individual investigator laboratories, include the following cores:
    - Microarray Core Laboratory
    - Tissue Culture/Viral Vector Laboratory
    - Analytical Chemistry
    - Protein Analysis (Biomolecular Resource Laboratory)
    - DNA Synthesis (Biomolecular Resource Laboratory)
    - Microscopy (fluorescence, transmission and scanning electron, confocal, time-lapse)
    - Tumor Tissue Core
    - Analytical Imaging
    - Biostatistics Unit

The Wake Forest Translational Science Institute (TSI), founded in 2007, is the hub of the research academic network within the institution focused on providing services and infrastructure for faculty to train in and conduct high quality clinical and translational research. The TSI also works with community organizations to improve the health of a largely underserved region encompassing central and western North Carolina, southwestern Virginia, and eastern Tennessee. This home for clinical and translational science is built on sustained commitment to, and leadership in, advancing health through discovery.

The Translational Science Institute's 6 Programs are designed to support specific areas of clinical and translational research needs. The TSI also partners with signature programs at Wake Forest, including the

Institute for Regenerative Medicine, Primate Models of Human Disease, and Population Science, as well as collaborates with a number of neighboring universities and institutions to provide innovative resources to researchers.

The TSI's programs provide broad-based and integrated services for translational researchers:

- *The Clinical Research Resources Program***:** The TSI Clinical Research Unit provides space, patient care, nutrition, and specimen processing support to clinical investigators with extramurally funded research projects and dedicates a portion of the budget to advancing projects with early-career faculty and investigators with pilot projects. The TSI Clinical Trials Office is responsible for the review, approval, and implementation of clinical trials, provides infrastructure to support and promote Medicare Coverage Analysis and appropriate research billing, maintains an accurate registry of all consented clinical trial participants, and develops tools and training for the clinical research community.
- *The Education, Training, and Career Development Program* provides training and support for promising early-career faculty through the TSI Research Academy and supports mentor development for mid-level faculty through the TSI Mentor Academy. These programs are designed to build and sustain strong career development programs for emerging and established investigators. Additionally, this program provides support to the broader academic community through the TSI Seminar Series, K-Award Writers' Series, Study Coordinator 101, Innovation Symposia, and Phlebotomy Training. **Dr. Miller** (PI) is a member of the TSI Mentor Academy and has access to the TSI's resources.
- *The Biomedical Informatics Program* supports faculty and research projects, providing a variety of services, including the REDCap database and survey development tool, the Profiles research networking tool, and custom development of programs and mobile applications to support pilot projects and secure, standardized access to comprehensive data through i2b2 and the Wake Forest Translational Data Warehouse.
- *The Program in Community Engagement and Implementation* promotes community-based research, increases best health practices, and reduces health disparities. It aims to engender trust, share ideas, empower mutual values, and achieve common language and purpose with community groups. The program works closely with community organizations to build sustainable working groups and proposals focused on community needs.
- *The Innovation Program* enhances access to translational technology, services, and training in the use of special applications, such as animal models, cell and systems biology, imaging, and proteomics and genomics to support translational research initiatives. This program works closely with the Wake Forest Innovation and Entrepreneurship Initiative to support faculty planning for and commercializing ideas emerging from academic research.
- *The Administrative Services Program* provides experienced administrators to reduce administrative burden by facilitating access to research resources and faculty expertise. Services include Research Navigation, which provides a central point of contact to obtain access to resources, services, and people and a Grant Management Core, which provides post-award support to manage all aspects of grant account activity and maintain fiscal compliance.

The Department of Internal Medicine (Thomas D. DuBose, Jr., MD, Department Chair) The Department of Internal Medicine is committed to the creation of new knowledge and the translation of these findings to the overall well-being of patients from our community, region and nation. The Department has approximately 140 fulltime faculty members and 5 Vice Chairs representing the areas of Research, Education, Administration, Clinical Service, and Quality Improvement provide counsel to Dr. DuBose. Twelve sections exist within the Department, including Cardiology, Endocrinology, Gastroenterology, General Internal Medicine, Gerontology, Hematology & Oncology, Hospital Medicine, Infectious Diseases, Molecular Medicine, Nephrology, Pulmonary & Critical Care, and Rheumatology. The Department historically emphasizes partnerships within areas that crosscut with research performed in other departments at the institution. Among these are human genetics, diabetes, asthma and lung disease, **cancer**, women's health, the biology of aging, substance abuse, and infection and immunity. The clinical activities of the Department of Internal Medicine provide extensive ambulatory facilities and serve patients with a broad diversity of human disease. Many patients participate in clinical research. Members of the Department represent the largest group of clinical investigators performing

research in the General Clinical Research Center. **David Miller, MD, MS** (PI) is an Associate Professor in the Section on General Internal Medicine.

The Department of Family Medicine (Michael Coates, MD, Department Chair) The research mission of the Department of Family and Community Medicine is designed to benefit patients and provide leadership for the academic discipline of Family Medicine. This is accomplished through the study of patients, family, communities and educational activities with active dissemination of this knowledge through local and national publications and presentations. The goals of the Department of Family and Community Medicine's Research Strategic Plan reflect its research mission statement as a department of community as well as family medicine. The Department's research goals comprise a comprehensive program that addresses issues of health and illness in community and clinic settings.

1. Build on current efforts in community research and expand our focus on primary and secondary prevention in the community.
2. Develop a clinical research program focused on promoting health and improving patient care.
3. Expand our community and clinical research programs that deal with the individual and the family as primary units of analysis, thus strengthening our unique mission of providing family medicine.

John Spangler, MD, is a co-investigator on this grant, and his appointment is in Family Medicine.

The Division of Public Health Sciences (Greg Burke, MD, MSc, Division Chair) The Department of Public Health Sciences was formed in 1989 from the Center for Prevention Research and Biometry, which had been founded in 1986 as evidence of the school's commitment to programs in prevention research. Thanks to the success and growth of the Department of Public Health Sciences, the Dean approved the creation of a Division of Public Health Sciences with three departments in January 2006.

The Division received more than $56 million in FY11 in extramural research funding from more than 90 collaborative research projects. Historically, the division has been ranked among the top two of similar groups nationally in NIH funding. The Division's overall goals are to further research programs in the areas of **biostatistics**, epidemiology, nutrition, and **health promotion/disease prevention**, and to strengthen research at the school by providing consultation in the development of research proposals, **study design**, **analysis** and other methodological issues. To achieve these goals, the Division is divided into three departments: a) **Biostatistical Sciences**, b) **Epidemiology and Prevention**, and c) **Social Sciences and Health Policy**.

The Division has ongoing programs in aging, adolescent health research, **cancer control**, cardiovascular disease, community interventions, diabetes, health related quality of life issues, nutrition, osteoporosis, renal disease and women's health. It also serves as the Coordinating Center for numerous multicenter studies. The Research Information Systems Unit (one of the sections within the Department of Biostatistical Sciences) specializes in state of the art research computing methodology.

The Department of Biostatistical Sciences (Walter Ambrosius, PhD, Department Chair) In 1986 the Center for Prevention Research and Biometry was established at Wake Forest School of Medicine and in 1989, the Section on Biostatistics in the Department of Public Health Sciences emerged from this unit. In 2006 the Section became the Department of Biostatistical Sciences in the newly formed Division of Public Health Sciences. The Department has grown steadily to 25 faculty members and 100 staff including biostatisticians, analyst/programmers, research information systems staff, project managers, data coordinators and support staff.

The faculty and staff in the Department conduct methodological research in survival analysis, sequential analyses, clinical trial design, categorical data analysis, analyses with missing data, measurement/misclassification errors, multivariate/longitudinal analysis, re-sampling techniques, robust regression, meta-analysis, psychometrics, regression diagnostics, quantitative epidemiology, statistical genetics, image analysis, machine learning, and health service methods.

The Department promotes basic, **clinical**, and **epidemiological** collaborative research of the highest methodological standards collaborating with investigators on study design, remote or centralized data entry systems, data management, quality assurance, data analysis, development of new statistical methods, sample size calculations, surveys and questionnaire development, publications, and manuscripts reviews. The

Department provides scientific programming, data systems design and management, web-based data capture, study coordination systems and networked communications, integrating strict quality control specifications. Faculty within the Department direct the Center for Public Health Genomics and biostatistics cores within the **Comprehensive Cancer Center** and the J. Paul Sticht Center on Aging.

Department faculty and staff are currently funded by 159 different and very diverse research projects and collaborate with 20 departments and centers outside of the Division of Public Health Sciences. The total requested awards for pending grants that involve DBS members reached $130 million in 2011 while total FTEs on funded applications has risen to 90. The awards for grants involving DBS members total $55 million in 2011. **Doug Case, PhD** (Co-I) and **Don Babcock** (Lead Analyst Programmer) are members of the Department of Biostatistical Sciences.

Department of Epidemiology and Prevention (Mara Vitolins, MD, PhD, Interim Chair) The Department of Epidemiology and Prevention is dedicated to research and teaching in the etiology and prevention of chronic disease. The ultimate goal of these efforts is to reduce death and disability and improve quality of life. Areas of research by 12 faculty and 55 staff include **cancer control**, **cancer epidemiology**, cardiovascular disease epidemiology, diabetes epidemiology, epidemiology of aging, demography of aging, genetic epidemiology, **health disparities, health services research** and nutrition. There is also a focus on clinical trials methodology; the Department houses both coordinating centers and clinical centers. The faculty has extensive experience with large, multicenter studies and collaborates with clinicians and basic scientists from a variety of other departments in the Medical School, as well as institutions across the US and abroad. **Dr. Miller** (PI) is cross-appointed to Epidemiology and Prevention.

Department of Social Sciences and Health Policy (Doug Easterling, PhD, Chair) The mission of the Department of Social Sciences and Health Policy is to improve the human condition through the application of social sciences and policy research to health and health care. Recognizing that health and healthcare represent complex challenges, the department is committed to collaborative, multidisciplinary and translational approaches to our research, education and community involvement. The Department of Social Sciences and Health Policy has expertise in health-related quality of life, prevention of substance abuse, medical effectiveness, health care outcomes research, psychosocial factors in health and disease, prevention of adolescent high-risk health behaviors, women's health issues, community interventions, and **cost-effectiveness analysis of medical treatments**. Areas of research interest of the 15 faculty members and 48 staff include adolescent health, alcohol, tobacco and drug use, community health, community interventions, **health services research**, health policy, psychometrics, women's health, cognitive health and aging, medical outcomes and quality of life issues. Members of the Department have headed or participated in multicenter studies of college drinking, underage drinking, CVD, dementia, and hypertension. **Kate Weaver, PhD, MPH,** a co-investigator on this grant, is an Assistant Professor in this department, and **Drs. Miller** (PI) and **Spangler** (Co-I) have cross-appointments.

Laboratory
Not applicable.

Animal
Not applicable.

Computer
Dr. Miller has an internet-accessible Dell computer with all software necessary for the completion of this project.

Computing Resources
Research computing is provided by the Department of Biostatistical Sciences, Section of Research Information Systems. Computing is supported through an FTE-based monthly fee which pays for the LAN access, network infrastructure, desktop support, CPU use, and disk storage. Core processors which form the computing base for the PHS Computing Facility include the following:
Unix/Linux Environment

- 2-SunFire V880 with 8 900 MHz CPU, 16 GB of RAM, and 430 GB internal storage

- 1-SunFire F12 with 12 105 0 MHz CPUs, 96 GB of RAM, and 576 GB internal storage
- 1-Sun E3500 with 6 450 MHz CPU, 3GB of RAM, and 170 GB internal storage
- Multiple RedHat Linux server running general purpose applications

Central Storage
Each of the UNIX systems listed above connect to the centralized storage system. This storage system is an EMC NS700. This storage enclosure contains 2.5 TB of storage resources with expansion up to 7 TB. One of the features of NS700 is hourly snapshots - backups to disk. These snapshots are taken throughout the day as a form of backup. The storage is also backed up nightly to tape.

UNIX Workstations (Sun Solaris)
In addition to the core Sun servers, RC also supports an integrated UNIX workstation configuration, configured as follows:

- 11-SunBlade 150 (user node)
- 1-SunBlade 2000 (user node)
- 2-Sun Enterprise 250 (user node)
- 2-Sun SparcStation Model 20 (user node)
- 15-Sun SparcStation Model 4/5 (user nodes, web server)
- 7-Sun UltraSparc Systems (user nodes)

High Performance Compute Cluster (HPCC)
Researchers may also leverage the HPCC systems. A HPCC system is a collection of servers running as one. Currently, multiple HPCC systems are available, including a 13 node IBM system, an 18 node Dell system, while some exploration is being done in the graphical processing unit (GPU) computing. All nodes are interconnect with high speed Ethernet connections and are attach to the SAN for storage.
Additional support equipment

- Dual Drive SDLT 30-Tape Library
- 2 HP 8150n LJ printers
- HP 8180n LJ printer
- HP 2550n color LJ printer
- Epson 755 LCD portable projector
- NEC NP510
- 8 Windows NT 4.0 application servers
- 5 Windows NT 4.0 web servers

Statistical Software
Statistical software supported includes SAS, S-Plus, Stata, StatXact, LogXact, MathType, CART, nQuery, Sudaan and SeqTrial. Editors available include VI, EMACS, Nedit and ed.

Windows Environment
The Division supports several hundred Windows based workstations and servers. A computer center houses over 15 Windows based Servers. These Division servers include database servers, web hosting servers, SAS servers, application servers, file servers, web site development servers, and workstation backup servers. The Division supports physical servers as well as VMWare-based virtual servers.

All servers that are available to the Internet, are secured in a DMZ zone, with two hardware firewalls. Local software firewalls are also used on each public server. Public server access is monitored at the hardware firewall location, by an outside monitoring company. The Division also monitors public servers, at the server software location, to help guarantee security. Operating system patches and hotfixes are implemented in a timely fashion, and can be managed remotely in an emergency.

All servers utilize RAID storage configurations for hardware reliability. Servers are backed up to tape, nightly, using our Legato Networker server backup system. The tape backup system has redundant SDLT Quantum drives with an on-line storage capacity of 7.5 Terabytes. The backup system is monitored daily by redundant administrative staff. Backup tapes are stored in a locked, fire-proof, storage vault, located outside the computer center, to ensure optimal disaster recovery. Additionally, a secure, off-site vault is used for tape storage.

In December of 2006 Wake Forest Baptist Health completed a fully operational, state-of-the-art, 5500 square foot data center in a new building designed for security and reliability. The data center is located at the new downtown campus of Wake Forest Baptist Health and provides a central presence for high-end computing (e.g., computing clusters), data storage facilities, centralized backup, and disaster recovery. The entire building's electrical needs are backed by a one Megawatt on-site generator. The data center provides a fully monitored environment for data processing equipment for the undergraduate campus of WFU, as well as a collocation facility for commercial and public service providers for the Piedmont Triad Research Park (PTRP) and the community, ensuring multiple high-bandwidth Internet paths and diverse state-of-the-art services. The Wake Forest Baptist Health networking environment is a fully converged, high speed, multi-use network supporting video streaming, VoIP, video teleconferencing and high-bandwidth display signage in addition to the typical data traffic along with a fully integrated wireless environment across all campuses WFU is one of the founding members of Internet II and utilizes the research and education network daily with our shared Virginia Tech-WFU School of Biomedical Engineering. WFU also provides piedmont North Carolina with a Regional Point of Presence (RPoP) called WinstonNet. This robust connection to Internet II and to the North Carolina Research and Education network (NCREN) is capable of 10 Gbps and is positioned to move to the Lambda Rail.

Office

Dr. Miller's academic office is located on the 3rd floor of Watlington Hall on the main campus of Wake Forest School of Medicine, 4 miles from the Downtown Health Plaza (see **Clinical** below), and 3 floors above one of the two endoscopy and colonoscopy suites where patients may be screened. The Section on General Internal Medicine provides secretarial support for its faculty, including Dr. Miller, and conference rooms are available for faculty to use for meetings, etc. His office is equipped with an internet-accessible computer networked to a shared printer, phone, and other customary office equipment. The co-investigators on this grant have similar office space, secretarial support, and conference room availability in various buildings at WFSM.

Clinical

Downtown Health Plaza: The Downtown Health Plaza (DHP), an outpatient clinic of North Carolina Baptist Hospital and NCQA-designated Patient-Centered Medical Home, is designed to meet the needs of a growing, increasingly diverse population. The Section of General Internal Medicine plays a major role in the delivery of care. The 47,600-square-foot medical facility, located at 1200 Martin Luther King Jr. Drive in Winston-Salem (about 4 miles from the main campus) serves all Forsyth County residents and surrounding communities. A tremendous community resource, it provides access to care not available to many otherwise. We will recruit patients from DHP. The DHP provides preventive and diagnostic services for adults (including OB/GYN services) and children and has financial counselors and Spanish interpreters on-site to meet the needs of its patients. (See **letters of support** from Robert Jones, Director of Downtown Health Plaza, and Jim Wofford, Medical Director)

Wake Forest Community Physicians (WFCP) was formed in 1994 as a group of neighborhood health care practices in an effort to stabilize and expand cost affordable, high quality, primary care services, into communities located throughout northwestern North Carolina. Community Physician practices are staffed by Board Certified Family Physicians, Internists, Pediatricians, Nurse Practitioners and Physician Assistants. The practices provide a wide range of services from general medicine to patient education. Providers enjoy the full range of primary care and have special interests in sports medicine, diabetes, hypertension, women's health, disease prevention, dermatology, nutrition, wound care, geriatrics and more. There are currently Community Physician practices located in six counties throughout northwestern North Carolina to include Forsyth, Davie, Davidson, Stokes, Surry and Wilkes. The WFCP health care team places strong emphasis on four key elements of a successful health care system:

- Available and accessible care in the local community
- Excellent quality care
- High patient satisfaction
- Cost affordable care in the most appropriate setting

In the current study, we will recruit patients from three Family Medicine and Internal Medicine community clinics (see attached **letter of support** from Vickie Russell, VP of Ambulatory Services).

Digestive Health Center

The Digestive Health Center of Wake Forest Baptist Health offers the region's most experienced experts in digestive diseases and the most advanced equipment and procedures to diagnose and treat gastrointestinal diseases. The Endoscopy Suite has state-of-the art equipment, a highly trained nursing staff, a full-service anesthesia team and an environment sensitive to patient comfort and privacy. More than 16,000 endoscopic procedures are performed each year. Patients come to the center from throughout the Southeast with digestive problems that range from the common to the very unusual and complex.

The Digestive Health Center on the main campus consists of 3 distinct areas:

- The Endoscopy Suite, where endoscopy and colonoscopy procedures are performed and the small bowel is examined by capsule endoscopy;
- The Gastrointestinal Neuromuscular Disorders Center, where acid pH, contraction, and electrical disorders of the esophagus and stomach are diagnosed by 24-hour pH and impedance monitoring, electrogastrography, esophageal manometry, anal rectal manometry, and breath tests; and
- The Advanced Endoscopy Center, where the most complex endoscopic procedures are performed. The Hepatobiliary and Pancreatic Disorders (HBP) Service, one of the most active in the state, currently performs approximately 700 therapeutic Endoscopic Retrograde Cholangiopancreatography (ERCP) procedures and 1,200 Endoscopic Ultrasounds (EUS) annually. ERCP provides access for diagnosis and therapy of diseases involving the bile ducts, gallbladder and pancreas. The EUS Service is one of the largest in the Southeast. EUS procedures examine the deeper layers of the gastrointestinal tract and adjacent lymph nodes to detect and biopsy masses. Among the unique services offered at the Digestive Health Center are combined EUS and ERCP under a single sedation at a single visit for evaluation of jaundice due to pancreas or biliary diseases.

The Gastroenterology Clinic, an outpatient clinic of North Carolina Baptist Hospital, has recently moved off-site to 500 Shepherd St., about 3 miles from the main campus. Consultations take place in a comfortable outpatient setting where gastrointestinal disorders are diagnosed and treated by our faculty. The clinic is in a spacious, state-of-the art facility, which is fully equipped and staffed for the outpatient management of digestive and hepatic diseases. Patients seen in this clinic represent the full range of secondary, tertiary, and quaternary consultation requests across the spectrum of gastroenterology and hepatology. In a separate suite in the same clinic is the Outpatient Endoscopy clinic. Services available include Endoscopy, Colonoscopy and Sigmoidoscopy. The facility is convenient for patients with an easily accessible endoscopy facility, convenient patient scheduling, free parking, results reported to patient at time of visit, prompt follow-up to referring physician, most major insurances accepted, full accreditation by AAAHC, and Medicare Certified.

Patients in this study who elect to be screened for colorectal cancer may be screened through WFBH's Digestive Health Center or GI Clinic, if they choose to be screened within the WFBH network.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
* First Name: David
Middle Name: Philip
* Last Name: Miller Jr
Suffix:

2. Human Subjects

Clinical Trial? ☐ No ☒ Yes

* Agency-Defined Phase III Clinical Trial? ☒ No ☐ Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix:
* First Name: Kim
Middle Name: O
* Last Name: Yates
Suffix:

* Phone Number: 3367163249 Fax Number: 3367164480
Email: nihawards@wfubmc.edu

* Title: Sr Grants/Contracts Adm

* Street1: Wake Forest University Health Sciences
Street2: Medical Center Boulevard
* City: Winston-Salem
County/Parish: Forsyth
* State: NC: North Carolina
Province:
* Country: USA: UNITED STATES
* Zip / Postal Code: 27157-0001

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4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Specific Aims

Colorectal cancer (CRC) screening saves lives, yet approximately 1 in 3 eligible Americans remain unscreened. Prior research has documented numerous barriers to CRC screening, including patient factors (lack of awareness of screening options, negative attitudes and beliefs, low health literacy), healthcare provider factors (lack of physician time, failure to recognize that screening is due), and system factors (scheduling barriers, failure to provide patient support). To achieve the highest screening rates possible, a multilevel intervention that is time-efficient, appropriate for varying literacy levels, and includes patient follow-up support is needed.

The explosion of user-friendly mobile devices offers an opportunity to develop innovative systems for improving CRC screening rates and clinic efficiency. Touch screen tablet devices can host interactive patient education software in a multimedia format that appeals to both low and high literacy audiences. In addition, tablet devices are portable and easy to integrate into a medical setting. Cell phones, which are now owned by 85% of American adults, offer an option for connecting with and supporting patients at all steps of the screening process.

The investigative team has considerable experience incorporating mHealth, or the use of mobile devices to enhance medical care, into primary care practices. This proposal will build on their expertise to evaluate the efficacy of an innovative multilevel mHealth CRC screening intervention (mCRC) designed for primary care practices. The conceptual framework for the mCRC intervention is based on Bandura's social cognitive model emphasizing reciprocal determinism, or the dynamic interaction of the person, the behavior, and the environment. The mCRC intervention includes a tablet CRC screening decision aid that will collect patient information, deliver a screening message, and allow patients to make a screening decision; "self-service" protocols that empower clinic staff to order screening tests requested by patients; and an automated, text messaging program that supports patients throughout the screening process.

We will evaluate the mCRC intervention in a randomized-controlled trial that will enroll 530 socioeconomically diverse English-speaking patients aged 50 – 74 years who are scheduled to see a primary care provider for a routine visit and are due for CRC screening. We will conduct the study at four community-based primary care practices affiliated with a large, academic medical center. To fully examine the mCRC intervention, the **Specific Aims** of this proposal are:

1) To test, in a patient-level randomized trial, the effect of the mCRC system on CRC screening rates (compared with an attention control program on healthy lifestyle habits) among patients due for screening who are attending primary care appointments.
   Hypothesis: Participants randomized to mCRC will be more likely to complete screening within 24 weeks compared with those randomized to the "healthy lifestyle" program.

2) To determine whether mCRC increases favorable patient attitudes and beliefs about screening, ability to form a screening choice, self-efficacy, intention, patient-provider CRC screening discussions, and test ordering; and whether these intermediate outcomes mediate effects of mCRC on test completion.
   Hypothesis: mCRC will increase all of these intermediate outcomes, and these effects will mediate most of the intervention effect on test completion.

3) To measure the additional cost of the mCRC system per patient screened compared with usual care. Costs will be measured from the perspective of the primary care clinic, including all equipment and staffing costs incurred before the screening event.
   Hypothesis: mCRC will increase screening at a cost of less than $100 per additional patient screened, an amount well within the range considered cost-effective.

Impact: The proposed study will impact CRC screening in two important ways: 1) by establishing the efficacy of a low-cost, easily implemented intervention that will facilitate CRC screening in primary care practices, using a novel tablet-based patient program and cell phone text messaging follow-up support, and 2) by delineating the mediators of CRC screening to guide the development of future interventions.

3. RESEARCH PLAN

3.1. Significance

Multilevel barriers result in underutilization of colorectal cancer (CRC) screening in the US. This proposal is significant because it will test a novel multilevel intervention to increase the use of colorectal cancer (CRC) screening, a life-saving but underutilized procedure in the United States. CRC is the 2th leading cause of cancer death in the United States.[1] CRC screening reduces both CRC incidence and its associated mortality.[2-4] Despite widespread guidelines recommending routine screening for CRC beginning at age 50, CRC screening remains underutilized in the United States with approximately 1 in 3 eligible Americans remaining unscreened.[4-8] Prior research has documented numerous significant barriers to CRC screening which can be divided into patient-specific factors and provider/system factors.

Many patients fear CRC screening tests, worrying the tests will be messy, embarrassing, painful, or lead to frightening cancer diagnoses.[9-13] Additionally, many patients fail to appreciate the threat of CRC or the benefits of screening.[14-16] Thus, many patients lack self-efficacy, or a belief that they are capable of completing the screening procedure.[9,11,12]

Healthcare provider and system barriers also contribute to low CRC screening rates. Healthcare providers frequently lack time to counsel patients or provide preventive services.[17-19] Provider lack of time is especially problematic given the variety of effective CRC screening tests that are available. Ideally, a patient and provider should agree upon a screening modality through shared decision-making, which requires time to adequately consider patients' specific concerns.[5,6] Unfortunately, busy providers often fail to fully relay information or review all available options with a patient.[20,21] Some providers may fail to address CRC screening at all, depriving patients of one of the most powerful motivators for receiving screening, a direct recommendation from their physician.[22,23]

Even if patients request CRC screening, simply scheduling a screening test can be a daunting task, requiring action from busy clinicians followed by handoffs to clinic staff and schedulers. Each handoff introduces a potential place for the system to break down. Furthermore, practices lack follow-up systems to confirm the tests were scheduled and completed. Allowing patients to "self-order" their screening would eliminate the risk of busy clinicians not addressing screening desires and would decrease the number of steps where an order could get dropped.

Another important system barrier to CRC screening is the lack of support for patients once the medical encounter is over. Many CRC screening tests require significant patient preparation in the form of dietary restrictions, sample collection procedures, and/or bowel preparation. Most (if not all) of these complex tasks must be completed by patients in their homes. However, the American medical system is poorly equipped to support patients if they have questions or encounter difficulties once they leave the office. This lack of support can result in failure to complete screening.

This proposal's mCRC multilevel intervention will address these patient and provider/system barriers in significant ways. A novel tablet-based CRC screening patient decision aid (iCHOICE) will inform patients of the need for screening, display patient vignettes to address fears and build self-efficacy, and feature physicians giving a direct recommendation to receive screening. New team care protocols will allow patients to "self-order" screening with the assistance of empowered non-physician staff. After the visit, a fully automated text messaging program (eSupport) will support patients throughout the screening process and provide early identification of any screening difficulties. By leveraging mHealth, or the use of new mobile technology in medical care, the mCRC system will enhance patient care while reducing healthcare provider workloads.

Inadequate health literacy magnifies many of the previously mentioned barriers to CRC screening. One-third of American's have inadequate health literacy, or difficulty understanding and using information to make healthcare decisions.[24] In one clinic-based cross-sectional survey, only 50% of limited literacy patients could name or describe any CRC screening test.[25] Other studies have demonstrated that low literacy patients are less likely to understand common screening tests such as Papanicolaou smears and mammograms, and they are less likely to receive preventive care interventions.[26-29]

Inadequate health literacy also hinders physician-patient communication. Low literacy patients report greater difficulty understanding their doctors.[30] At the same time, low literacy patients are less likely to ask questions during medical encounters.[31] These barriers to care translate into worse health outcomes for low literacy patients, including higher mortality.[32,33] Interventions that can deliver information effectively to all patients regardless of literacy level and encourage them to be active participants in their medical care are urgently needed.

Current CRC screening interventions may not be appropriate for the one-third of Americans with low-literacy skills. Although printed patient education materials on CRC screening are voluminous, most are written at grade levels inaccessible to low literacy patients.[34] Even web-based educational programs are developed at high reading levels and incorporate audio or video components only one-third of the time.[35]

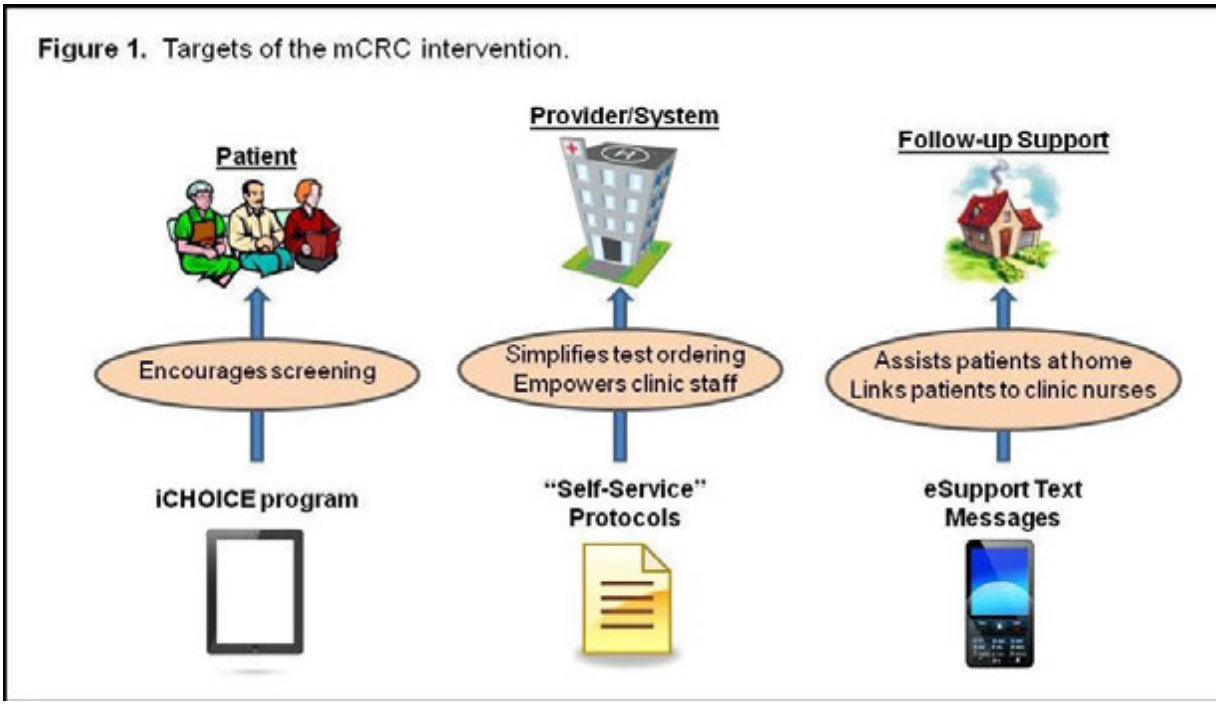
We have developed and tested a web-based CRC screening decision aid specifically designed for a mixed literacy audience.[36] We have based this multilevel intervention's tablet CRC program (iCHOICE) on this validated decision aid. Furthermore, we have designed every aspect of the intervention for ease of use by low literacy patients while also appealing to high literacy users. Additionally, the intervention encourages patients to discuss their CRC screening needs and preferences with their healthcare providers.

3.2. Innovation

This proposal is innovative with respect to its overall design and individual components:

Multilevel design. Numerous single-level CRC screening interventions have focused on patient, provider, or health system factors, with only modest success. Examples include patient or provider reminders, patient education, direct mailings of test kits, and patient navigators.[37] However, CRC screening occurs in a complex, multilevel environment which illustrates the need for interventions that target multiple levels to improve outcomes.[38,39] Only a few multilevel CRC screening interventions have been published in the medical literature, but they have shown promising results, particularly in underserved populations.[40-43] Therefore, to achieve the greatest impact on CRC screening, we designed mCRC as a synergistic multilevel intervention. The mCRC intervention has three distinct targets: 1) the *individual patient* with the iCHOICE program, 2) the *provider/system* with "self-service" protocols, and 3) *follow-up support* with eSupport text messaging (see **Figure 1**).

Figure 1. Targets of the mCRC intervention.



Sensitivity to diverse literacy levels. Acknowledging the crucial role of health literacy in mediating health outcomes, we designed the mCRC intervention to be appropriate for low literacy patients while also appealing to high literacy patients.

Focus on decreasing provider workload. Recognizing healthcare providers' limited time, we designed mCRC to ease provider workload by offloading common tasks to mobile technology. We also included "self-service" protocols that empower non-physician staff to play a more active role in screening, thereby maximizing each team member's contributions to patient care.

User-friendly mobile technology. Our prior experience integrating mobile technology in primary care guided the development of this proposal. The mCRC system leverages mHealth, or the use of mobile technology to enhance patient care. First, mCRC includes a novel tablet-based CRC screening patient decision aid (iCHOICE) coupled with "self-service" protocols that allow clinic staff to order screening. Second, we designed a very innovative automated text-messaging system (eSupport) to support patients throughout the screening process and provide early detection of potential barriers (such as a lost prescription for a colonoscopy prep).

Text messaging support. Approximately 85% of American adults now own a cell phone, making text messaging a new option for connecting with patients.[44] Prior studies examining text messaging interventions to help patients with behavior change have shown promising results.[45] Our mCRC study will be one of the first to incorporate text-messaging support for patients undergoing cancer screening.

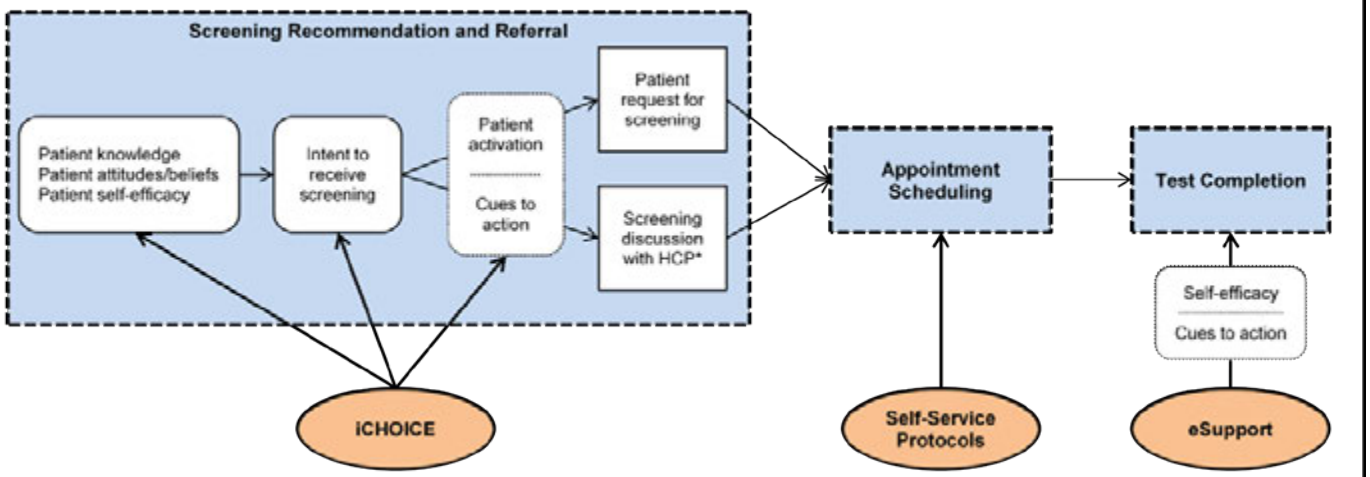
3.3. Approach

We will evaluate the mCRC intervention in a randomized controlled trial that will enroll 530 English-speaking patients aged 50 – 74 years who are scheduled to see a primary care provider for a routine visit and are due for CRC screening. The study will be conducted at 4 community-based primary care practices affiliated with a large academic medical center in North Carolina. The study clinics serve a population that is racially and socioeconomically diverse. The primary outcome of interest is patient completion of a CRC screening test within 24 weeks. We will measure intermediate outcomes for each level of the intervention.

3.3.A. Organizing Framework

The mCRC intervention is informed by the social cognitive model and will target the key steps of the CRC screening process outlined by Price et al.[38,46,47] This multilevel intervention is based on reciprocal determinism, or the dynamic interaction of the person, the behavior, and the environment in which the behavior is performed. The intervention will target not only the knowledge, beliefs and self-efficacy of the individual patient who is due for screening, but also the medical system to facilitate receipt of referrals and testing supplies and to provide cues to action to complete CRC screening (**Figure 2**).

Figure 2. Mediation model for the mCRC intervention



3.3.B. Preliminary Studies

Our multidisciplinary research team has rich expertise in cancer control, technology assisted-instruction, health literacy, educational interventions, behavioral science, and cost-effectiveness. Our extensive experience collaborating and conducting research in these areas will ensure the successful completion of the mCRC study. The theme of cancer control is woven through much of our prior work described in the sections below.

3.3.B.i. Educational patient-directed technology in healthcare (web, computer, tablet, and mobile phone). Our experience studying the use of patient-directed technology in healthcare informed the development of this proposal's mCRC intervention. Miller (PI) systematically examined the use of computer-assisted instruction in patient care and collaborated with Denizard-Thompson (Co-Investigator) on an analysis of text-messaging by low-income urban patients.[48,49] Additionally, Miller and Denizard-Thompson completed a pilot study of a series of novel iPod-based patient education programs for anticoagulation management.[50] The patients rated the visual quality and educational experience very highly. Of note, the pilot study was conducted in a community-based clinic that will also be used in this proposal's mCRC trial.

We have also created and studied multiple patient education programs. Miller created and tested a computer-based multimedia patient education program about fecal occult blood testing (FOBT) in a low income population, with Case (Co-I) assisting with the study design and analysis.[51] Funded by an American Cancer Society Career Development Award, Miller (with Pignone and Spangler as mentors; consultant and Co-I on this project respectively) later developed and tested a web-based CRC screening decision aid based on an earlier video-tape decision aid (CHOICE) created by Pignone.[36,52] Regardless of health literacy level, patients randomized to the web-CHOICE program were more likely to form a screening decision and more likely to desire screening (see **Table 1**). However, only one-third of patients who wanted immediate screening had a screening test ordered. The mCRC intervention will address this process gap by allowing "self-service" ordering of screening tests.

Table 1. Results from testing of web-based CHOICE program

	Patient Literacy Level	
	Low/Limited (n=72)	Adequate (n=59)
Able to complete program with:		
2 episodes of assistance or less	62 (93%)	59 (100%)
1 episode of assistance or less	45 (67%)	56 (95%)
No assistance	31 (46%)	43 (73%)
Agreed with:		
Program was easy to use	71 (99%)	59 (100%)
Program was easy to understand	72 (100%)	59 (100%)
Would recommend this program	71 (99%)	59 (100%)
Preferred program to a brochure	72 (100%)	57 (98%)
Increased intention to receive screening*	24 (60%)	14 (42%)
Able to make a screening decision	55 (77%)	55 (93%)
Desired immediate screening	29 (40%)	28 (47%)

*Analysis limited to those who were not in the maximal stage of intention at baseline

In this proposal, we will create an even more user-friendly interface based on patient feedback. We will move the CHOICE decision aid to an iPad platform (iCHOICE). We have already developed a beta-version of the iCHOICE program using rapid-revision cycles based on feedback from patients attending a primary care practice. iCHOICE includes video, survey questions programmed with large intuitive buttons, and optional audio narration. We pilot-tested iCHOICE in a convenience sample of 40 patients at two community-based primary care practices, one of which serves a socioeconomically disadvantaged population and will serve as a study clinic for the mCRC study. All participants successfully completed the program, and 90% completed the program with one episode of assistance or less (see **Table 2**).

Table 2. Pilot testing of iCHOICE prototype (iPad)

	Patient Literacy Level	
	Low/Limited (n=8)	Adequate (n=32)
Able to complete program with:		
1 episode of assistance or less	8 (100%)	28 (88%)
No assistance	7 (88%)	23 (72%)
Agreed with:		
Program was easy to understand	8 (100%)	32 (100%)
I learned something important	6 (85%)	30 (97%)
Questions were easy to read	8 (100%)	32 (100%)
Buttons were easy to touch	7 (88%)	30 (94%)
Preferred the program to a brochure	7 (88%)	26 (87%)*
CRC screening knowledge after iCHOICE program†		
Increased quiz score	5 (63%)	15 (48%)
No change in quiz score	3 (38%)	15 (48%)
Decreased quiz score	0 (0%)	1 (3%)

*2 participants answered "don't know" to the preference question
†Knowledge assessed by 5-item quiz

3.3.B.ii. Health literacy. One third of Americans have low health literacy, highlighting the importance of ensuring that interventions are appropriate for low literacy audiences.[24] Miller and Pignone have studied the

effects of health literacy on CRC screening knowledge.[25] In our prior randomized controlled trial, we demonstrated that the web-CHOICE CRC screening decision aid was equally effective in both low and high literacy patients.[36] Pignone has also studied low literacy interventions for patients with diabetes and heart failure, and completed a systematic review of interventions to improve health outcomes for low literacy patients.[53-56]

3.3.B.iii. Educational interventions and behavioral science. Spangler has worked extensively in cancer prevention and health promotion, focusing on both health professional training and patient education. He has been PI on two NCI R25 cancer education awards targeting medical students, one focusing on tobacco intervention (R25CA0965662), and the other on weight management counseling and the relationship of obesity to cancer (R25CA117887). Miller was co-investigator on the latter project, and both projects involved wide-ranging development of web-based educational modules. In addition, Spangler is Co-PI on a project developing coronary vascular disease prevention messages for Lumbee Indian women (R21 MD005995).

Miller also has been co-investigator on a project that developed a web-based training program for evidence-based prescribing (SmartPrescribe.org) and is co-investigator on a current award to develop a comprehensive substance abuse curriculum for primary care residencies (U79T1020278). Denizard-Thompson brings additional expertise in ambulatory education and health disparities to this project, as Wake Forest's Internal Medicine Residency Program's Director of Ambulatory Education, Residency Clinic Director, and a member of the Society of General Internal Medicine's Health Disparities Task Force. She will use this expertise to help create culturally appropriate health messages for this project's eSupport system.

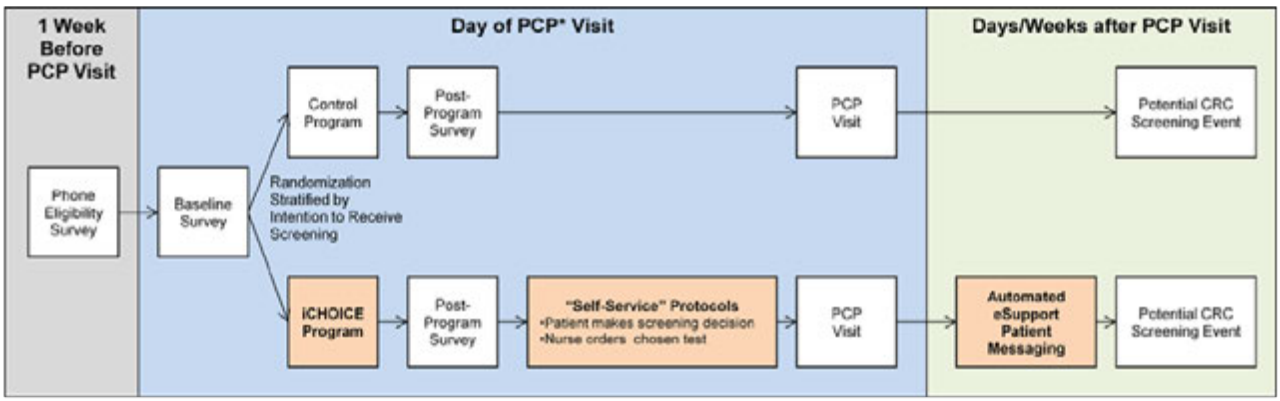
Weaver (Co-I) has expertise in designing health behavior surveys and interventions to promote health behavior change in medical populations.[57-59] Dr. Weaver is leading an ongoing smoking cessation intervention based on social cognitive theory for lung cancer patients through the Wake Forest University Community Clinical Oncology Program, one of only 6 NCI-funded research bases that develops clinical trials for cancer prevention, detection, and treatment to be performed in community oncology practices.

3.3.B.iv. Cost-effectiveness. Troyer (Co-I), a health economist who has conducted several cost-effectiveness studies, will be primarily responsible for the cost analysis of the mCRC study. Troyer was Co-PI on a clinical trial funded by the Administration on Aging (90AM2665) that considered the cost-effectiveness of a nutrition intervention for older adults with cardiovascular disease.[60] In addition, she is currently part of a trial funded by the Agency for Healthcare Research and Quality (R18 HS018519) to study the cost-effectiveness associated with physician use of a quantitative pretest probability instrument for acute coronary syndrome or pulmonary embolism, which is likely to reduce cardiopulmonary imaging in the emergency department.

3.3.C. **Overview of the mCRC Multilevel Intervention and RCT Design**

The mCRC system includes a tablet-based CRC screening decision aid (iCHOICE) that provides education and allows patients to choose a specific CRC screening test, "self-service" protocols that empower practice staff to order CRC screening requested by patients, and an automated messaging system to support patients (eSupport) as they complete the screening process. An overview of the study design is below (**Figure 3**).

Figure 3. Overview of mCRC study design



3.3.D. **Patient Eligibility**

The trial will enroll English-speaking patients aged 50 – 74 years who are scheduled to see a primary care provider for a routine (i.e., non-urgent care) visit and are due for CRC screening (no colonoscopy within the prior 10 years, no flexible sigmoidoscopy within the prior 5 years, and no fecal blood testing [FOBT or FIT] within the prior 12 months).[4,5] Exclusion criteria include specific CRC risk factors (first degree relative with CRC, personal history of adenomatous polyps, personal history of inflammatory bowel disease, recent blood in stools) and patients with an obvious physical or mental disability that would prevent them from interacting with a tablet device.

3.3.E. **Study Sites and Recruitment**

The study will be conducted at 4 community-based primary care practices affiliated with Wake Forest Baptist Health (see **letters of support** from Russell, Jones, and Wofford). One clinic (the Downtown Health Plaza or DHP) is a faculty-resident internal medicine practice that serves a primarily socioeconomically disadvantaged patient population with a limited health literacy prevalence of approximately 50% as measured in prior studies.[25,36] The other three practices are members of Wake Forest Community Physicians (WFCP), a network of family medicine and internal medicine clinics serving a higher socioeconomic population. The DHP and WFCP practices share a single comprehensive electronic health record (EPIC) which simplifies data collection. Pilot data at the DHP site indicates that approximately 57% (9/16) of age eligible patients are overdue for CRC screening. Based on published data for the state of North Carolina, we estimate that 31% of WFCP age eligible patients will be overdue for screening.[8] Demographics of the clinic population across all sites are shown in **Table 3**.

Table 3. Study site patient demographics, FY2012

	DHP	WFCP
Annual Visits	29,289	102,307 (11 practices)
Number of Unique Patients	10,227	31,762
Insurance Status, n (%)		
Uninsured	2,023 (20%)	2,258 (7%)
Medicaid	3,674 (36%)	3,377 (11%)
Medicare	2,290 (22%)	9,803 (31%)
Commercial/Other	2,240 (22%)	16,324 (51%)
Patient Gender, n (%)		
Male	3,916 (38%)	13,459 (42%)
Female	6,309 (62%)	18,300 (58%)
Race/Ethnicity, n (%)		
African-American	6,280 (61%)	4,195 (13%)
Hispanic/Latino	1,236 (12%)	917 (3%)
White	2,557 (25%)	25,681 (81%)
Other	154 (2%)	969 (3%)

DHP = Downtown Health Plaza
WFCP = Wake Forest Community Physicians

The clinics have agreed to provide us with on-going access to their electronic appointment schedules (which include patient age) to identify potentially eligible patients. Using these schedules, a research assistant (RA) will call patients in our target age group one week in advance of their appointments to inform them of the study and determine eligibility. Up to 3 contact attempts will be made for each potentially eligible patient.

To mask the purpose of the study, potential participants will be told the study seeks to "determine the best way to teach patients about important health topics." Furthermore, the eligibility survey will contain distracter items about other health behaviors to avoid an intense focus on CRC screening which may affect subsequent patient behavior.

Eligible patients will be instructed to arrive to the clinic 45 minutes in advance of their scheduled medical appointment to enroll in the study. Enrolled participants will receive a $10 gift card after completing the post-program survey on the day of enrollment, and a $5 gift card after completing the 24-week follow-up telephone survey.

3.3.F. **Baseline Survey and Randomization**

The RA will meet with each eligible patient in a quiet, private space at each study clinic 45 minutes before their scheduled medical visits to obtain informed consent and administer the baseline survey using a tablet device (iPad). The baseline survey is programmed to allow patients to self-administer the survey with the RA present to provide assistance as needed. In pilot testing of the survey program, all 40 patients were able to complete it in approximately 6 – 8 minutes and reported it was easy to understand.

As detailed in **Section 3.3.I**, the baseline survey assesses patient demographics (including the single-question health literacy screen),[61] attitudes and beliefs about CRC screening, self-efficacy, and intention to receive CRC

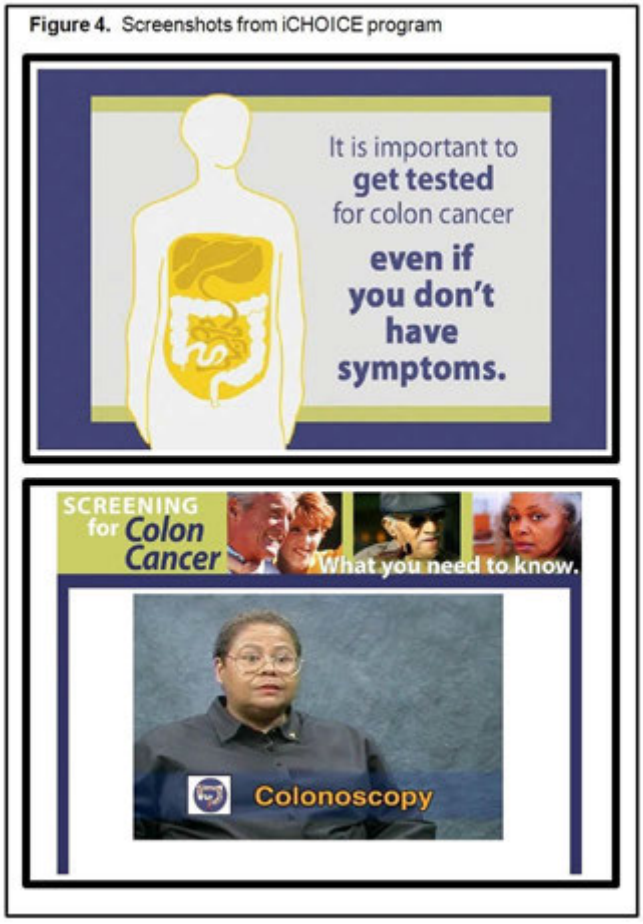
screening. Intention to receive screening is measured with two items: 1) "Do you plan to be screened for colon cancer in the next 6 months?", and 2) "Do you plan to ask your doctor for colon cancer screening at today's visit?" Following methods we previously published, responses to these two items map each patient to an intention stage according to the TransTheoretical model (Precontemplation, Contemplation, or Preparation for Action).[36,62] Using a block randomization scheme, the tablet program will randomize each patient to either the control arm or intervention arm, stratified by their baseline intention (see **Section 3.3.J**. below for details).

3.3.G.**mCRC Intervention Description**

The mCRC intervention includes an iPad CRC screening decision aid (iCHOICE), "self-service" protocols to allow office staff to order CRC screening tests, and an automated text-messaging support system (eSupport).

3.3.G.i. iPad CRC screening decision aid (iCHOICE). The iPad CRC screening decision aid (iCHOICE) is a multimedia program combining easy to read text, audio narration, and video to overcome potential literacy barriers. iCHOICE includes a 6 minute video reviewing current CRC screening recommendations, the rationale for screening, and the available screening tests. Physician-narrated sections (one middle-aged African American male, and one middle-aged white female) raise awareness about vulnerability for CRC, the importance of early detection, and provide a direct recommendation to receive screening, one of the most powerful patient motivators.[63] Patient vignettes explicitly model screening test utilization, address negative attitudes and beliefs, and support self-efficacy to complete screening (**Figure 4**). iCHOICE is based on a previously validated web-based CRC screening patient decision aid (web-CHOICE) viewable at http://intmedweb.wakehealth.edu/choice/choice.html.[36] After the video, iCHOICE asks patients if they would like to be screened for CRC and what test they prefer. The screening options are tailored to the most commonly ordered screening tests in each study clinic (FOBT/FIT, colonoscopy, and in one clinic, flexible sigmoidoscopy). The iCHOICE program also asks patients to enter their cell phone number for follow-up support (see eSupport, **Section 3.3.G.iii.** below). The iCHOICE program closes by encouraging patients to discuss their screening decision, concerns, or need for more information with their healthcare provider.

Figure 4. Screenshots from iCHOICE program



3.3.G.ii. "Self-service" protocols. The closing screen of the iCHOICE program displays the patient's screening selection. If the patient chose to be screened, the RA will notify the study clinic staff of the patient's desired screening test. The study clinics have agreed to approve protocols that empower nurses to distribute FOBT/FIT test kits and/or refer patients for flexible sigmoidoscopy or colonoscopy as indicated by patients' choices (see attached **letters of support**). When a test is given or referral placed, the clinic nurse will send the patient's primary care provider a notification via the electronic health record to give him/her the opportunity to override the screening order if needed. A provider override is expected to be a rare occurrence, but could be needed if, for example, a patient was known to have a contraindication to endoscopy.

3.3.G.iii. Automated text messaging system (eSupport). eSupport is a branching algorithm electronic communication program designed to support patients throughout the screening process. It is modeled after other novel text messaging programs, which assisted patients with behavior change.[64-66] The iCHOICE program (**Section 3.3.G.i.**) will automatically download each patient's screening decision and cell phone number into the eSupport program.

We designed the eSupport system to provide *cues to action* critical to the successful completion of CRC screening and to facilitate *self-efficacy* by connecting patients with medical staff to assist with problem solving if barriers arise (such as a missing prescription for a colonoscopy bowel preparation). For patients who chose screening, eSupport sends automated text messages at critical times in the screening process. eSupport will send each patient the first message the day after enrollment to welcome them to eSupport and reinforce their screening decision. Each electronic message gives patients the option to request a callback from a clinic nurse to address questions or concerns. In proof of concept pilot testing, we used Google Voice to send 7 patients a text message, and we received 5 confirmatory replies.

The timing of eSupport's messages will vary according to the screening test ordered. A sample schedule for eSupport messages is shown in **Table 4**. For patients who chose endoscopic screening, eSupport will send a text in one week asking them to reply with the date of their screening appointment. Using a text matching algorithm, eSupport will interpret the reply, send a confirmatory text to the patient to ensure the correct date was decoded, and then store the screening date in the system to trigger future messages. If the date is not verified on two attempts, an automated message will be sent to the study team to contact the patient by phone to acquire the appointment date. If a patient chooses not to be screened in the iCHOICE program, eSupport will send them a text message the day after enrollment to encourage them to reconsider screening and give them the option to request a nurse callback.

Table 4. Representative eSupport messages for colonoscopy screening

Message Timing	Message Content*
Day after visit	• Reinforcement of screening decision • Notice that another message will be sent in 1 week
Week after visit	• Inquiry to see if colonoscopy scheduled • Cue to respond with appointment date
1 week before colonoscopy	• Reinforcement of the screening decision • Inquire to see if bowel prep received
3 days before colonoscopy	• Self-efficacy support regarding prep • Reminder to start clear liquid diet
Day before colonoscopy	• Self-efficacy support • Review of transportation needs

*All messages will include the option to request a callback from a clinic nurse.

Development of eSupport system

Specific messages and timing of the messages will be developed with the assistance of 4 patient focus groups (n= 5-8 each) (see **Section 3.3.M** Timeline). Each focus group will meet for 90 minutes. Two focus groups will be comprised of patients who are overdue for CRC screening, and two focus groups will be comprised of patients who are current on their screening. One set of focus groups will be recruited from the DHP, a practice serving primarily socioeconomically disadvantaged patients, and the other set of focus groups will be recruited from the WFCP practices which serve a predominantly privately insured population (see **Section 3.3.E**). Focus groups will be held at a convenient time and community location, and food will be provided. Participants will receive $25 for participating.

A trained moderator will lead each focus group using a moderator's guide developed by the study team. Separate guides will be developed for the patients who have and have not completed CRC screening. Topics to be explored will include attitudes about CRC screening, biggest challenges encountered or anticipated during CRC screening, sources of information/advice/assistance regarding CRC screening, thoughts about receiving electronic communications from health care providers, and perceived helpfulness of potential messages. Focus groups will be audio recorded and transcribed and the results qualitatively analyzed to ensure the eSupport messages address anticipated barriers, are culturally acceptable, are understandable to individuals of varying literacy levels, and are delivered at the optimal times. Babcock, lead analyst programmer on this proposal, will program the eSupport system and provide technical assistance as needed.

3.3.H. **Control Program**

Patients randomized to the control arm will view a 6-minute iPad program on the "4 Principles of Healthy Living", a set of lifestyle habits proven to reduce mortality.[67,68] Participants in both the control and intervention arms will complete the same baseline and post-program surveys to measure changes in intention to receive screening and patient ability to choose a screening test. However, control group participants will not self-order a screening test or be entered into the eSupport program.

3.3.I. Outcome Measures

Primary and secondary outcomes will be assessed throughout the study (**Table 5**).

Table 5. Overview of outcomes and how they will be collected

Outcome	Measurement Methods						
	Baseline Survey	Post-P Survey*	Day+1 Survey	eSupport Database	Chart Reviews	Week 24 Survey	Nursing Survey
Demographics	X						
Health literacy	X						
CRC screening attitudes/beliefs	X	X					
Intention to receive screening	X	X					
Self-efficacy	X	X					
Ability to make a screening decision		X					
CRC screening discussions			X				
Receipt of eSupport messages				X		X	
Patient requests for clinic callbacks				X			
CRC screening ordering					X	X	
CRC screening completion					X	X	
Patient calls to clinic					X	X	
Nursing time per call							X

*Post-P Survey = Post-Program Survey

Baseline Survey. The baseline survey assesses patient demographics. Additionally, health literacy will be estimated using the single-item health literacy screening question ("How confident are you filling out medical forms by yourself?").[61] We will measure CRC screening attitudes and beliefs with items modified from a validated instrument.[69] Specific items address the perceived benefits of screening (i.e., ability to detect cancer early, ability to save lives) and patients' fears and concerns (i.e., fear of receiving bad news, fear that tests are painful, concerns that tests are embarrassing). We will measure self-efficacy to complete CRC screening with a previously validated 4-item instrument from Vernon et al.[70] Patient intention to receive screening (categorized as Precontemplation, Contemplation, or Preparation for Action) will be measured using the two items described in detail in **Section 3.3.F**. To avoid influencing subsequent behavior, we will mask the intention of the study by including several distracter items such as questions about tobacco use and other preventive medicine interventions.

Post-Program Survey. The post-program survey will include the same attitude/belief, self-efficacy and intention to receive screening items as the baseline survey. Comparing the baseline and post-program survey responses will allow us to compute differences attributed to the program (Specific Aim 2). Patient's ability to make a screening decision will be assessed with the item: "If you decided to be screened for colon cancer, which test would you prefer?" (Specific Aim 2). Possible responses to this item will include "I don't know enough to decide," an option that was chosen by 45% of control group respondents in a prior study.[36]

Day+1 Telephone Survey. The day after enrollment, a study team member blinded to the randomization will call each participant to determine if a CRC screening discussion occurred during the subsequent primary care visit, who initiated the conversation, the content of the conversation, and the end result of the conversation (Specific Aim 2). Participants who are not reached by phone after 5 attempts will be mailed a paper copy of the survey with a stamped return envelope. Any missing Day+1 surveys will be considered as "no conversation occurred."

eSupport Database. The eSupport database will be analyzed to determine: 1) the number of participants who confirmed receiving the Day+1 eSupport message, 2) the accuracy of patients' entering their endoscopic screening dates and the number of patients requiring a phone call to determine the date, and 3) the number of clinic callbacks participants requested.

Chart Reviews. A blinded chart review will be performed after 24 weeks to determine whether CRC screening was ordered, was completed, and the results of the screening within the WFBH system (Specific Aim 1). All patient phone calls to the study clinics are logged as phone notes in the EHR. The number of patient calls related to CRC screening will be counted. All charts will be reviewed by two data collectors, and any disagreements in coding will be resolved by consensus. Comparing the number of patient calls in the

control arm versus the mCRC arm will allow us to determine the excess number of calls attributed to patient activation from the mCRC system, which would result in added nursing time cost (Specific Aim 3).

Week 24 Telephone Survey. A study team member blinded to randomization will call each participant at 24 weeks to conduct a brief end-of-study survey that will assess whether CRC screening was ordered outside the WFBH system, and if so, the type of screening ordered, whether screening was completed, and the results of the screening (Specific Aim 1). Copies of outside records will be requested to verify all patient-reported screening. If records are not obtainable or if the records show no evidence of screening, the patient will be considered "unscreened." The survey will also assess whether patients received any eSupport messages, an estimate of the number of messages received, the perceived helpfulness of the messages, and the number and nature of calls to the clinic triggered by the messages. Identical to the Day+1 Survey, participants who are not reached by phone after 5 attempts will be mailed a paper survey with a stamped return envelope. Participants will receive a $5 gift card after completing this survey.

Nursing Survey. A study team member will review the eSupport database twice a week to identify participants who requested a clinic callback. A research assistant will ask the nurse who responded to the callback request to estimate the amount of time the patient call required. These estimates will be used to calculate an average time per call for each clinic, for use in cost analyses (Specific Aim 3).

3.3.J. Statistical Considerations

Study Design. We will use a randomized, parallel group design to assess the effect of the mCRC system on six-month screening rates in men and women who are due for CRC screening. Participants will be stratified by site and intention to receive screening and randomized within strata to receive the mCRC system or a control program with equal probability, as described below. The primary outcome is the completion of an appropriate screening test within 24 weeks of randomization. Completion of screening will be defined as chart evidence of a completed test. Patient-reported screening completed outside the WFBH system will be verified by review of outside records. Patients lost to follow-up (i.e., no visits occurring after 24 weeks and patient unable to be reached by telephone) will be considered "unscreened." Secondary outcomes are screening tests ordered, patient attitudes and beliefs about CRC screening, patient ability to state a screening preference, self-efficacy, intention to receive screening, patient/provider CRC screening discussions, and cost of the mCRC system. Analysis will be carried out based on 'intent to treat.'

Statistical Analyses. Descriptive reports will consist of summary statistics (means, standard deviations, proportions, etc.) for patient characteristics and outcome measures by treatment arm, actual versus projected accrual, participation by the various sites, and quality control information (retention, missing data, etc.). Tables, graphs, and charts will be used to illustrate the data when appropriate. This report will be reviewed at regular study staff meetings, occurring every 2 weeks during study enrollment and then monthly.

Aim 1. The primary hypothesis will be assessed using a logistic regression model with successful CRC screening (Y/N) as the outcome, treatment arm as the primary independent variable, and the stratification factors (site and screening intent) as covariates as per the design. In secondary analyses, we will assess the effects of age, gender, race and ethnicity, health literacy, and other patient characteristics on screening rates, and arm-by-covariate interactions will be included to determine if the effect of the mCRC system differs depending on levels of the covariates. The Hosmer-Lemeshow statistic will be used to assess goodness of fit. This same strategy will be used to assess the impact of the mCRC system on screening test orders.

Aim 2. As secondary objectives, we will assess the effect of the mCRC system on the patient's attitudes and beliefs about CRC screening, ability to state a screening preference, self-efficacy, intention to receive screening, and the occurrence of patient/provider CRC screening discussions. In addition, we will examine if the effect of the mCRC system on screening rates is mediated by these five secondary measures. The impact of the mCRC system on each measure will be assessed using linear or logistic regression as described above for the primary outcome. Mediation analysis will be used to determine the degree to which each secondary measure (separately and collectively) are responsible for (or mediate) the effect of the mCRC system on CRC screening. Methods have been proposed to overcome shortcomings in the original mediation methods proposed by Baron and Kenny,[71] and these are compared by MacKinnon et al and summarized by

Krause et al.[72,73] Several of these methods had similar operating characteristics, such as assessing the product of the coefficients describing the relationship between treatment and the mediator and the mediator and the outcome,[74,75] and jointly testing the two coefficients.[76] Most commonly, mediation analyses are done using continuous outcomes and covariates. However, for this aim, the outcome and many of the possible mediators are dichotomous. While some researchers[77] have suggested that the methods developed for continuous measures can be used for dichotomous measures, with appropriate modifications, others[78] have suggested that those models are not appropriate, and Hicks and Tingley[79] have implemented an alternative approach for causal mediation analysis in a STATA program. These various approaches will be examined in assessing the mediation effect in this study.

Aim 3. The U.S. Preventive Services Task Force has found sufficient cost-effectiveness evidence to strongly recommend colorectal screening for adults 50 years of age or older.[80] The cost-effectiveness of colorectal screening programs has been clearly established by other researchers.[81] In this study, the cost analysis will focus on the additional cost of the mCRC screening system to the primary care clinic prior to the screening event. As such, patient costs will not be considered. Key costs to the clinic include costs of hardware and hardware support, software support, and nursing staff time spent answering questions related to the eSupport system. Time spent discussing the screening process during the routine visit will not be captured, as the length of the patient visit is not likely to increase as a result of the intervention. Costs for staff time will be computed using time estimates from the Nursing Survey (described in **Section 3.3.I**) and national average wage values for nursing staff from the Bureau of Labor Statistics. We hypothesize that the additional cost will be less than $100 per patient screened, an amount well within the range of what is considered cost-effective and on the low end of the cost of other CRC screening interventions.[82,83]

Randomization. Patients will be stratified by site and intention to receive screening and randomized within strata into one of the two treatment arms, the mCRC or control program, with equal probability using variably sized permuted block randomization. Block randomization will be used to ensure approximately equal accrual to each arm from each stratum over time. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from past assignments. Treatment assignments will be generated using nQuery Advisor 6.0 and stored in tables which will be accessed by the iPad program.

Sample Size/Power. Our prior CRC screening study in a socioeconomically disadvantaged population found a screening rate in the control group of 14%.[36] Because the mCRC trial will recruit patients from a mixture of clinics, some with fewer barriers to care, we assume our control group will have a higher screening rate of 20%, similar to the control group rate seen in Pignone's CRC trial conducted at three community-based clinics.[52] Assuming a control group screening rate of 20%, the total sample size for this study will be 530 (approximately 265 in each group); this number will provide 80% power for detecting a 12% absolute difference in screening rates (20% to 32%) at the 5% two-sided level of significance, conservatively assuming a 15% loss to follow-up. While we expect the control screening rate to be around 20%, it is possible that it will be higher or lower. **Table 6** shows the differences we will be able to detect with 80% and 90% power with a sample size of 530 for control rates ranging from 10% - 30%, again assuming a 15% loss to follow-up.

Table 6. Differences detectable with 80% and 90% power as a function of the screening rate in the control group, assuming a 15% loss to follow-up

Control Screening Rate	Detectable Difference	
	80%	90%
.10	.098	.115
.15	.111	.129
.20	.120	.139
.25	.127	.147
.30	.131	.152

In our prior RCT of 264 patients, we enrolled approximately 6 participants a week in a single clinic with a high prevalence of unscreened patients.[36] The mCRC study includes some clinics with fewer barriers to care resulting in higher baseline screening rates and therefore fewer eligible participants. Therefore, even though we will be recruiting from multiple clinics, we anticipate we will accrue approximately 5 – 6 patients a week, requiring 2 years to accrue our full sample of 530 participants. The patient population of the study clinics and estimated proportion that will be due for screening are described in **Section 3.3.E**.

Data Management. The survey data and participant interaction data will be temporarily stored on the iPad using secure Advanced Encryption Standard 256 bit encryption (AES-256) to protect personal health information. The iPad software uses an opportunistic store and forward mechanism we have developed to

send that data to the central data storage server whenever it can establish contact. Upon positive confirmation that the data have been sent and received, they are removed from the iPad, thus further reducing any possible risk of data exposure. This allows the application to operate with our without immediate network connection. This process is automatic and no special action by the application user is required. All study site databases will be backed up nightly using BackBlaze (San Mateo, CA), an encrypted offsite backup service. Study meta-data is collected using a custom designed web based data entry facility. The data is stored in a Microsoft SQL Server database that resides in Wake Forest's server farm. These servers are backed up each day by Wake Information Systems. The servers reside on their own protected internal network further protecting the data.

3.3.K. **Limitations**

We considered several potential limitations in designing this study. We will guard against a Hawthorne effect (or the risk that the simple act of being in a study will increase screening rates) by masking the purpose of the study with distracter questions unrelated to CRC screening. The consent form will also describe the purpose of the study as "examining the best way to teach patients about important health topics", a strategy we have employed in prior work.[36] We strongly considered a cluster study design to minimize the chance of contamination. However, because study staff will administer all study materials, the risk of contamination is low. Furthermore, a patient-level trial is more powerful and will yield more evenly randomized intervention and control arms.

To ensure our study will achieve its planned 80% power, we have allowed for some drop out in our sample size calculations. We have also recruited a large system of clinics which will let us enroll patients from additional sites if an individual clinic drops out of the study. Lastly, to guard against any potential data loss in the event of a network failure, we have programmed the iPad surveys to retain all data locally until the network connection is re-established, and all databases are backed up nightly.

3.3.L. **Dissemination**

Following completion of the study, we will make the iCHOICE and eSupport programs freely available. A technical support e-mail contact will be provided. Findings from this study will be presented at national scientific meetings where we will also provide information for downloading the programs. In addition, we will work with several national organizations (i.e., American Academy of Family Physicians, American College of Physicians, Society of General Internal Medicine) to advertise the programs on their websites and list-serves.

We designed iCHOICE and eSupport specifically for ease of dissemination. iCHOICE runs on the iPad platform as an app. eSupport will run on a reliable yet inexpensive Apple Mac Mini Server whose data is backed up using the BackBlaze encrypted offsite backup service for disaster recovery. This same approach can be easily implemented by even the smallest clinics, as this equipment and service is widely available at low cost. In addition, the server back-end technology is Java-based and can be easily adapted to fit the likely infrastructure of larger healthcare enterprises if preferred to the Mac Mini "standalone appliance" approach.

3.3.M. **Study Timeline**

	Year 1				Year 2				Year 3				Year 4			
Study Task	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Control program video creation	X	X														
eSupport technical programming	X	X														
eSupport focus groups		X														
eSupport message programming		X	X													
Study team prep/training			X													
Trial enrollment				X	X	X	X	X	X	X	X					
Data collection				X	X	X	X	X	X	X	X	X	X			
Data cleaning & analysis				X	X	X	X	X	X	X	X	X	X	X	X	
Study dissemination															X	X

6. PROTECTION OF HUMAN SUBJECTS

6.1. RISKS TO HUMAN SUBJECTS

A. HUMAN SUBJECTS INVOLVEMENT, CHARACTERISTICS, AND DESIGN:

Describe the proposed involvement of human subjects.

Human subjects will be involved in 2 aspects of this project: focus groups and a subsequent randomized-controlled trial. To inform the final development of the intervention's text messaging component, we will conduct 4 focus groups of 5 – 8 patients each. Each focus group will meet for 90 minutes at a convenient time and location.

In the subsequent mCRC trial, we will recruit participants from 4 community-based primary care practices. Participants will be adults aged 50 – 74 years who are scheduled for a routine medical visit. A research assistant will telephone potentially eligible patients approximately one week in advance of their scheduled visits to inform them of the study, and if they are interested, administer a telephone eligibility questionnaire. The research assistant will meet eligible patients at the clinic site 45 minutes in advance of their scheduled medical appointments to obtain written informed consent and enroll them in the study.

All participants will complete a baseline survey, and then be randomized to either the mCRC intervention or an attention control arm. Participants in the mCRC arm will interact with a tablet-based colorectal cancer (CRC) screening patient decision aid and indicate whether or not they would like to receive CRC screening. Those participants who elect to receive CRC screening will receive occasional follow-up text messages to provide ongoing support throughout the screening process. Participants randomized to the control arm will interact with a tablet-based patient education program about healthy lifestyle principles (i.e., maintain a healthy body weight, eat fresh fruits and vegetables daily, etc.). A research assistant will administer brief follow-up telephone surveys to all participants in both arms the day after study enrollment and at 24 weeks after enrollment.

Describe and justify the characteristics of the subject population.

We will recruit participants 50 – 74 years old from the 4 study clinics to participate in the focus groups. In the subsequent trial, we will enroll 530 participants aged 50 – 74 years old who are due for CRC screening according to guidelines published by the United States Preventive Services Task Force. We require a total sample size of 530 patients to detect an absolute difference of 12% in the prevalence of receiving a CRC screening test with 80% power, after assuming a 15% loss to follow-up. A 12% increase in screening rates is a clinically significant outcome. We chose the age range of 50 – 74 years old to match the recommended ages for routine CRC screening.

Describe and justify the sampling plan.

To allow us to hear from patients who may face differing barriers to CRC screening, we will conduct 2 focus groups of patients who are overdue for CRC screening and 2 focus groups of patients who are current on their screening. Each focus group will be comprised of 5 – 8 patients aged 50 – 74 years who were recruited from the 4 study clinics.

In the mCRC trial that follows, patients aged 50 – 74 years old will be identified from the appointment schedules of the study clinics. A research assistant will telephone these potentially eligible patients approximately one week in advance of their scheduled appointments to inform them of the study and invite them to participate. Participants will receive a $10 gift card after all study activities on the day of enrollment are complete. Participants completing the 24 week telephone survey will be given a final $5 gift card.

Inclusion criteria include age 50 – 74 years old (the target age for routine CRC screening), and being due for CRC screening according to guidelines published by the United States Preventive Services Task Force. We will exclude patients with risk factors or symptoms that would place them at increased risk for CRC, and therefore make them ineligible for routine screening (these high risk patients would require different CRC screening strategies or diagnostic testing). Specific exclusion criteria include: a family history of CRC in a first degree relative, a personal history of CRC or adenomatous polyps, a personal history of inflammatory bowel disease, and the presence of recent visible blood in bowel movements. We also will exclude any patients who have a physical or mental illness that would prevent them from interacting with the tablet-based CRC screening patient decision aid, because these patients would be unable to complete the mCRC intervention. In addition, all participants must be able to read and understand English. Non-English speaking patients account for < 5% of the study clinics' combined target patient population. If the mCRC intervention is proven effective, a subsequent Spanish version will be created.

Explain the rationale for the involvement of special vulnerable populations.

The only vulnerable populations we will include in our study are those with low health literacy and the economically disadvantaged. Approximately one-third of Americans have limited health literacy, highlighting the importance of ensuring that interventions are tested in populations that include those with low health literacy. Additionally, the poor face increased barriers to CRC screening and should not be excluded from interventions designed to make screening easier.

Describe procedures for assignment to a study group.

Participants will be block randomized to either the mCRC intervention or the attention control arm. The tablet computer will perform the randomization after participants complete the baseline study survey. Human subjects research will not be performed at any collaborating sites.

B. SOURCES OF MATERIALS:

Describe the research material obtained from living individuals, any data that will be collected from human subjects for the project(s) described in the application, who will have access to individually identifiable private information about human subjects, and how records, and/or data are collected, managed, and protected.

Participants will complete study surveys that will assess their basic demographic information, health literacy level, attitudes and beliefs about CRC screening, intention to receive CRC screening, ability to make a screening decision, self-efficacy to complete CRC screening, whether they discussed CRC screening with their healthcare providers, and whether they completed CRC screening. Participants in the mCRC intervention arm will also provide their cell phone number so they may receive follow-up support text messages. Research assistants will complete chart reviews to determine if CRC test ordering and completion was documented, and whether participants called the study clinic with any CRC screening related questions (as evidenced by telephone notes).

All participants will be assigned a study ID number that will be linked to their personally identifiable information in a separate database stored on a secured, password protected computer and accessible only to key study personnel. All datasets for analysis will include the study ID number and not any personally identifiable information, other than appointment dates which will be required for data interpretation. Participants' cell phone numbers will reside in the computer program that generates the automated follow-up support text messages. The text messaging program will run on a password protected computer located in a secure location at each study clinic. All databases will be backed up nightly using software with encryption technology.

C. POTENTIAL RISKS:

Describe the potential risks to subjects, and assess their likelihood and seriousness to the human subjects. Describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

The study intervention includes a tablet-based patient decision aid and follow-up supportive text messages. Accordingly, the potential risk to participants is minimal. The main risk would be loss of data confidentiality. To protect patient confidentiality, all participants will be assigned a study ID allowing us to remove their names and other identifiable information (other than appointment dates) from the study datasets. Even if data confidentiality were compromised, the risk to participants would remain small since the data we are obtaining for study purposes is not highly sensitive.

The only alternative to participation in this study would be not to participate. This decision will not impact the participant's medical care or treatment in any way.

6.2. ADEQUACY OF PROTECTION AGAINST RISKS

A. RECRUITMENT AND INFORMED CONSENT:

Describe plans for the recruitment of subjects, and the process for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent.

The Wake Forest Institutional Review Board will approve the study, including the informed consent document. All study team members will maintain certification in human subjects protection. The study clinics

will provide the study team with access to their electronic appointment schedules. The team will query the appointment schedules to identify patients aged 50 – 74 years old (the target age for this study). Research assistants trained in human subjects protection will call these potentially eligible participants approximately one week in advance of their scheduled appointments to inform them of the study and invite them to participate. Eligible participants will meet the research assistant at the study clinic 45 minutes in advance of their scheduled appointments with their healthcare provider. The research assistant will verbally review the informed consent form with the participant, provide each participant with a copy of the informed consent document, and only after the participant endorses full understanding obtain written consent. Participants will be informed that we are testing novel methods to inform patients of important health topics, the surveys they will be asked to complete, and that they may receive follow-up informational text messages. We will also inform participants that study team members will review their charts to gather data.

B. PROTECTIONS AGAINST RISK:

Describe planned procedures for protecting against or minimizing potential risks. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of clinical trials and adverse event reporting.

The only anticipated risk participants face is loss of data confidentiality. To protect against this risk, all participants will be assigned a study ID number which will be used in all study datasets in place of identifying information (with the exception of appointment dates which will be needed for data analysis). All study datasets will be stored in encrypted, password protected files located on password protected computers in secure locations. The master dataset linking patient identifiers to the study ID numbers will be kept in a separate secured dataset on a password protected computer accessible only to key study personnel.

The research team will regularly monitor the security of the datasets and study computers. Given the above mentioned security measures, we estimate the risk of loss of participant confidentiality is very low. In the event of any loss of data confidentiality or any other adverse effect from participating in the study, the research team will promptly report the event to the IRB and the NIH.

6.3.<u>POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS</u>

Discuss the potential benefits of the research to research participants and others.

Participants in the intervention arm of the study will learn about CRC screening, be encouraged to receive screening, and receive follow-up support throughout the screening process. Accordingly, participants in the intervention arm are likely to benefit by receiving a recommended, effective screening test. Participants in the attention control arm also have the potential to benefit from their exposure to the control program which will review recommended lifestyle habits for maintaining good health.

6.4.<u>IMPORTANCE OF THE KNOWLEDGE TO BE GAINED</u>

Discuss the importance of the knowledge gained or to be gained as a result of the proposed research. Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

CRC is the second leading cause of cancer-related death in the United States. CRC screening reduces CRC mortality, and is recommended by the United States Preventive Services Task Force. This study will yield information critical to increasing the proportion of patients who receive this life-saving preventive care. Specifically, this study will yield knowledge that will help healthcare providers and systems determine ways to improve the delivery of CRC screening to their patients. The only significant risk faced by participants in this study is loss of confidentiality. The importance of the knowledge to be gained from this study, and the potential benefit individual participants will receive from their involvement in this study, outweigh this small risk.

6.5.<u>DATA AND SAFETY MONITORING PLAN</u>

Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported.

As mentioned previously, the only anticipated risk to participants in this study is loss of data confidentiality. The research team will form an internal Data and Safety Monitoring committee, comprised of the PI, Project Manager, study statistician (Case), and study programmer (Babcock). This committee will monitor the integrity of the study data systems on an ongoing basis to protect against any security weakness or breaches. In addition, the study team will immediately apprise the PI of any problems so that appropriate

action can be taken in a timely manner. The PI will promptly review any participant or other-reported concerns regarding the study or an adverse event. The PI will report any loss of data confidentiality or other adverse event to the Wake Forest IRB and the NIH within 2 business days of the discovery the event.

6.6. CLINICALTRIALS.GOV REQUIREMENTS

Although this study does not meet the requirements for mandatory registration with ClinicalTrials.gov, the PI will register this study with ClinicalTrials.gov before subject recruitment commences.

7. INCLUSION OF WOMEN AND MINORITIES

7.1. Targeted/planned distribution of subjects by sex/gender and racial/ethnic groups.

The mCRC study will enroll 530 patients. Because patients will be recruited from community-based primary care clinics, the planned distribution of participants will approximate the demographics of the clinic populations. Similar to other primary care practices nationwide, the majority of patients in the clinic population are female. Therefore, we plan to enroll more women than men (309 women and 221 men).

We chose one study clinic specifically because it serves a majority minority population, and we wanted to ensure racial diversity in our study sample. However, because the study clinics are located in western North Carolina, over 97% of the study clinic's patients are either white or African American. Approximately 5% of the clinic population is of Hispanic or Latino ethnicity, and our targeted study sample will match this distribution. By racial categories, our targeted sample will include approximately 71% white, 26% African American, 1% American Indian/Alaska Native, 2% Asian, and < 1% Native Hawaiian/Pacific Islander (a very rare population in western North Carolina). (See attached Targeted/Planned Enrollment Table.)

7.2. Description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design.

We will invite all patients aged 50 – 74 years old who are scheduled for a routine primary care visit at one of the study clinics to participate. Colorectal cancer (CRC) affects both genders equally and all races. Therefore, we will recruit all gender and racial/ethnic groups. As mentioned above, we did choose one study clinic specifically because most of its patients are members of a minority population, and we wanted to increase minority representation in our study.

7.3. Rationale for proposed exclusion of any sex/gender or racial/ethnic group.

We will not exclude any gender or racial/ethnic groups from our study. However, because non-English speaking patients account for less than 5% of the study clinics' population, it is not practical at this time to make multiple language versions of the intervention and study materials. Therefore, our inclusion criteria include the ability to speak and understand English. Provided the intervention proves successful, we will create a subsequent version in Spanish. Of note, we will enroll English-speaking Hispanic or Latino patients in this study.

7.4. Proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Because the selected the study clinics to achieve racial diversity, and because the majority of primary care patients are female, we do not anticipate difficulties in enrolling a diverse patient population. Nonetheless, we will monitor our planned recruitment and if we find we are not meeting our enrollment targets for a specific subpopulation, our Research Assistants will begin preferentially calling patients from those underrepresented groups to invite them to participate. We will be recruiting patients from computer generated appointment schedules provided to us by the study clinics. The appointment schedules will include the patient's racial/ethnicity group to aid targeted recruitment efforts.

8. Targeted/Planned Enrollment Table

See link below for updated notice:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-086.html

9. INCLUSION OF CHILDREN

Present an acceptable justification for the exclusion.

Children are excluded from this study because the research topic (routine CRC screening) is not relevant to children. According to guidelines from the United States Preventive Services Task Force, routine screening for CRC is recommended beginning at age 50. Therefore, participants must be at least 50 years old to participate in this study.

13. Consortium / Contractual Arrangements: The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

University of North Carolina at Charlotte:

Jennifer Troyer, Ph.D., Professor and Chair of Economics, as Co-investigator