

Supplement

Choice Architecture and Colorectal Cancer Screening Outreach

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## 23 Initial Protocol

24

### 25 **Abstract**

26 A 3-arm randomized trial assessing whether the rate of completion of colorectal cancer screening  
27 is increased when patients receive a sequential choice in screening options (colonoscopy followed  
28 by Fecal Immunochemical Testing (FIT)) or an active choice (FIT or colonoscopy offered  
29 together) versus colonoscopy alone. The targeted population is patients within the University City  
30 and Valley Forge Community Care Associates (CCA) practices at the University of Pennsylvania  
31 Health System.

32

### 33 **Study Instruments**

34 The primary endpoint being evaluated is the rate of participation in colorectal cancer screening between  
35 the two intervention arms (Sequential Choice, Active Choice) versus the control arm (colonoscopy only).  
36 The FIT is a well validated tool for colorectal cancer screening and is one of the screening modalities  
37 recommended by the USPSTF. The control arm will be sent a letter inviting them to schedule screening  
38 colonoscopy directly through the Gastroenterology Call Center. If not scheduled within 4 weeks, subjects  
39 will receive a mailed reminder to call to schedule. The Sequential Choice arm will be sent the same initial  
40 outreach as the control arm. If not scheduled within 4 weeks, subjects will receive a mailed reminder  
41 including the call center number as well as the option to complete a FIT kit mailed along with the  
42 reminder. The Active Choice arm of the study will be sent a letter offering the choice of Colonoscopy or  
43 completion of the FIT kit included with the initial mailing. If subjects in this group have not either  
44 scheduled colonoscopy nor completed FIT within 4 weeks, they will receive a mailed reminder to call to  
45 schedule colonoscopy or to complete the original mailed FIT.

46

47 A sub-sample of 90 subjects will be called to complete a questionnaire over the phone 4 months after  
48 initial outreach was mailed. The subjects will be asked to confirm their eligibility (e.g. that they had not  
49 had CRC screening within the USPSTF CRC screening guidelines) and provide additional demographic and  
50 socioeconomic information so that we can better understand what populations, if any, may have  
51 differential response rates. We will also ask them about their perception of the impact and design of  
52 CRC screening outreach. Demographic and socioeconomic questions are modified from demographic  
53 questions on the Behavioral Risk Factor Surveillance System survey, administered by the Centers for  
54 Disease Control and Prevention. See attached sub-sample questionnaire.

55

### 56 **Group Modifications**

57 For subjects in the Control (Colonoscopy only) arm of the study, the post outreach phone questionnaires  
58 will not include questions regarding mailed FIT.

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### 61 **Method for Assigning Subjects to Groups**

62 Subjects will be randomly assigned Study ID numbers and then randomized to one of three study arms  
63 stratified by the two practice locations (University City and Valley Forge) using a computer-generated  
64 randomization algorithm. The research coordinator will record the randomization assignments on a  
65 master list which will be maintained by the research coordinator on a password protected computer in a  
66 locked office. The research coordinator and research assistants will assemble the mailings based on this  
67 master list.

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**Administration of Surveys and/or Process**

90 subjects will be randomly selected for the questionnaire. We anticipate the post outreach questionnaires to take 10 minutes to complete over the phone. The research staff will make no more than three attempts to speak directly with the subject. Based on a previous project where we reached about 50% of patients via phone call, we anticipate reaching approximately 45 subjects (15 in each arm) to complete this sub-sample questionnaire.

**Administration of Surveys**

All subjects will complete a baseline and post-intervention survey. The baseline survey will collect basic demographics and baseline medication adherence and blood pressure monitoring frequency and be conducted over the phone after the participant has been consented. The post-intervention survey will collect similar adherence and monitoring information, as well as qualitative data regarding patient perceptions about the interventions. The post-intervention survey will be completed at the in-person 4 month visit. These surveys should take no more than 15 minutes to complete. Demographic and socio-economic questions are modified from demographic questions on the Behavioral Risk Factor Surveillance System survey, administered by the Centers for Disease Control and Prevention.

**Objectives**

1.1 Objectives

The specific aim of this study is to assess the effectiveness of two different mailed outreach activities (sequential choice of colonoscopy then FIT, active choice of colonoscopy and FIT) versus colonoscopy only in increasing participation in CRC screening.

1.2 Primary Outcome Variable

The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial outreach

1.3 Secondary Outcome Variable(s)

The secondary outcome is the choice of screening test between FIT and colonoscopy.

Additional outcomes include demographic and socioeconomic characteristics of subjects who participate, as well as exploratory qualitative data regarding experience with the different outreach methodologies. Additional outcome is the percentage of FIT screening results that are positive, percentage of those positive FIT tests that receive follow-up diagnostic colonoscopy, and percentage of colonoscopies that find adenomas, advanced adenomas, and cancer.

**Background**

1.1 Program Goals

Despite effective strategies for prevention, early detection, and treatment, colorectal cancer (CRC) is the third most common type of cancer and second leading cause of cancer death in the United States. The US Preventive Services Task Force (USPSTF) recommends routine CRC screening for all individuals aged 50-75; yet, despite aggressive public health efforts to promote screening, national rates are still suboptimal at 59-64%.

Colonoscopy is the predominant form of screening in this country due to perceived effectiveness by providers, but it entails a significant cost in time, resources, and perceived discomfort. The fecal

118 immunochemical test (FIT) is an attractive screening option as it is less invasive than traditional lower  
119 endoscopy and can be mailed to patients to complete at home. A recent study has shown that offering  
120 the choice of colonoscopy or stool-based testing in a clinic setting increases screening rates, but receipt  
121 of colonoscopy has better durability since stool-based testing has to occur every year.  
122

123 In this study, we will be using population-based outreach screening to evaluate the feasibility of a  
124 proactive screening program to promote fecal immunochemical testing (FIT) and/or colonoscopy  
125 through mailed outreach by leveraging principles of behavioral economics. We know that mailed FIT  
126 outreach circumvents the need for an office visit and eliminates friction in the screening process, since  
127 patients can perform testing at home in minutes, but it is not clear how patients may respond to  
128 different choice architecture about FIT versus colonoscopy as they have historically been seen as  
129 competing, rather than complementary strategies. Behavioral economics suggests that choice  
130 architecture may also impact response based on how the intervention is designed. For example, offering  
131 the choice of colonoscopy with the mailed FIT kit may enhance participation (as compared to offering  
132 colonoscopy alone) since it makes the decision an active choice, where the patient is choosing between  
133 two options as opposed to the traditional opt-in approach. Offering mailed FIT after colonoscopy, as is  
134 currently the standard during in-office visits, may also increase participation. By evaluating the  
135 effectiveness of these alternative choice approaches, we will enhance the public health capacity and  
136 efficiency to increase CRC screening uptake and reduce preventable death from this disease.  
137

## 138 **Statistical Considerations**

### 139 1.1 Power and sample size

140 Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data  
141 Store. Through other projects in primary care practices at Penn Medicine we found the accuracy rate of  
142 the EMR algorithm to be approximately 75%. As such, we anticipate we will have enough patients to  
143 enroll 423 subjects (and randomize 141 into each arm). We estimate a base return rate for the  
144 colonoscopy only (control) arm to be 5%, and we will consider a meaningful increase in response rate to  
145 be 10 percentage points for both the sequential choice and active choice arms as compared to control.  
146 This will be sufficient sample size to detect a 10 percentage point increase in response rate using a two-  
147 tailed chi-square test with 80% power and a 5% level of significance.

### 148 1.2 Data analysis

149 The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial  
150 outreach. We will conduct a chi-square analysis using Stata to compare arms 2 and 3 to arm 1 separately  
151 using intent-to-treat protocol. We will also compare arms 2 and 3 as a secondary analysis. We will  
152 quantitatively analyze the choice of screening test and evaluate the survey results by study arm. As  
153 exploratory analyses, we will evaluate response by practice location, age, gender, race/ethnicity, and  
154 income at the level of zip code.  
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156  
157 Analysis will be conducted by blinded members of the research team at least four months after the last  
158 FIT is mailed.  
159

## 160 **Study Design**

### 161 1.1 Design

162 Randomized: Subjects will be randomly assigned Study ID numbers and then randomized to one of

163 three study arms stratified by practice location using a computer-generated randomization algorithm.  
164 The research coordinator will record the randomization assignments on a master list which will be  
165 maintained on a password protected computer in a locked office. The research coordinator and research  
166 assistants will assemble the mailings based on this master list.

167  
168 Blinding: The investigators will be blinded to the randomization assignment. The research coordinator  
169 and research assistants will be unblinded. The blind may be broken for clinical care purposes.

170

### 171 1.2 Consent Process

172 Waiver of consent for the main portion of this pilot study is being requested, as this study involves no  
173 more than minimal risk to subjects. Colonoscopy and FIT are clinically available and utilized tests used to  
174 screen for colorectal cancer. The outreach methods in the three arms are all offered during routine  
175 clinical care either at Penn Medicine or other health systems across the country. The only research  
176 related activity is the randomization of subjects to different outreach strategies that would typically  
177 occur in practice. Subjects will receive information about the risks and benefits of FIT through our  
178 outreach and about the  
179 risk and benefits of colonoscopy from the physician performing the procedure.

180

181 Subjects rights and welfare will not be adversely affected by the waiver of authorization and consent.  
182 All subjects will have the opportunity to voluntarily participate in CRC screening. Arm 1 (Colonoscopy  
183 only) will receive screening by colonoscopy if they elect. Arm 2 (Sequential Choice) will receive CRC  
184 screening either by Colonoscopy or FIT if they elect. Arm 3 (Active Choice) will receive CRC  
185 screening either by Colonoscopy or FIT if they elect. Each arm has the opportunity to engage in CRC  
186 screening through routine care as well.

187

188 We believe that we would not be able to practically conduct the research without waiver of consent. If  
189 we had to obtain either written or verbal consent ahead of time, it would substantially limit our study  
190 population and it may alter their participation in the intervention. Thus, we would only learn about the  
191 response rate for patients who we were able to speak to for consent. This, would limit the  
192 generalizability to practice. Obtaining waiver of consent would allow us to avoid the potential  
193 selection/volunteer bias for inclusion of patients particularly interested in screening that can occur when  
194 consent is required. Since our main objective is to understand the potential influence varying outreach  
195 strategies on subject behavior, we believe that obtaining consent would compromise our primary  
196 objective. Additionally, we have received waiver of consent for similar studies related to colorectal  
197 cancer screening outreach.

198

199 Verbal consent will be obtained from the subsample with whom we plan to conduct post intervention  
200 interviews (see script).

201

### 202 **Study Duration**

203 We anticipate conducting chart reviews for two months, mailed outreach and reminder follow-up for  
204 two months, waiting for completion of screening for an additional 4 months, and sub sample interview,  
205 data analysis and manuscript compilation for 4 months. Thus, we anticipate this pilot project to last 12  
206 months. Project date of the proposed study: July 1, 2017 - June 30, 2018.

207

### 208 **Resources Necessary for Human Research Protections**

209 Shivan Mehta is the PI of this study. He is a gastroenterologist and assistant professor of medicine at the

210 Perelman School of Medicine. All members of the research team have completed CITI human subjects  
211 research training. The Research Coordinator will provide thorough education and training to the  
212 Research Assistants to ensure that they are well-prepared to carry out the duties in their job  
213 descriptions. Additionally, the Research Coordinator will audit 10% of the electronic medical record  
214 reviews that the Research Assistants complete, in order to check for compliance. Detailed Standard  
215 Operating Procedure documents for the project will be accessible to all members of the research team,  
216 which will keep research staff informed about the protocol and their related duties. There are adequate  
217 facilities to conduct the research; all research staff have adequate office space on the UPenn campus.

218

### 219 **Target Population**

220 Eligibility Criteria: The study population includes patients between 50 to 74 years old who have received  
221 care at the University City and Valley Forge CCA practices, are due for screening, and are asymptomatic  
222 for CRC.

223

### 224 **Subjects Enrolled by Penn Researchers**

225 423

226

### 227 **Subjects Enrolled by Collaborating Researchers**

228 0

229

### 230 **Accrual**

231 Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data  
232 Store. Through other projects in primary care practices at Penn Medicine we found the accuracy rate of  
233 the EMR algorithm to be approximately 75%. As such, we anticipate we will have enough patients to  
234 enroll 423 subjects (and randomize 141 into each arm). We estimate a base return rate for the  
235 colonoscopy only (control) arm to be 5%, and we will consider a meaningful increase in response rate  
236 to be 10 percentage points for both the sequential choice and active choice arms as compared to  
237 control.

238 This will be sufficient sample size to detect a 10 percentage point increase in response rate using a two-  
239 tailed chi-square test with 80% power and a 5% level of significance.

240

### 241 **Key Inclusion Criteria**

242 1. Between 50 and 74 years old

243 2. Has had at least two office visits at the University City or Valley Forge CCA practice within the past 2  
244 years (at time of chart review)

245 3. Due for colorectal cancer (CRC) screening

246 4. Asymptomatic for CRC

247 5. Zip code listed in PennChart as part of the subjects address is within the Philadelphia-Wilmington-  
248 Camden Metropolitan Statistical Area

249 6. Has a primary care provider who is a University City or valley Forge Family Medicine provider

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255 **Key Exclusion Criteria**

- 256 1. Has had prior colonoscopy within 10 years, sigmoidoscopy within 5 years, and FOBT/FIT within twelve  
257 months of the chart review (We will exclude patients who self-report undergoing any of the above  
258 procedures)
- 259 2. Has a history of CRC
- 260 3. Has a history of other GI cancer
- 261 4. Has history of confirmed Inflammatory Bowel Disease (IBD) (e.g. Crohns disease, ulcerative colitis)
- 262 Irritable bowel syndrome does not exclude patients.
- 263 5. Has history of colitis other than Crohns disease or ulcerative colitis
- 264 6. Has had a colectomy
- 265 7. Has a relative that has been diagnosed with CRC
- 266 8. Has been diagnosed with Lynch Syndrome (i.e. HNPCC)
- 267 9. Has been diagnosed with Familial Adenomatous Polyposis (FAP)
- 268 10. Has iron deficiency anemia
- 269 11. Has history of lower GI bleeding
- 270 12. Has metastatic (Stage IV) blood or solid tumor cancer
- 271 13. Has end stage renal disease
- 272 14. Has had congestive heart failure
- 273 15. Has dementia
- 274 16. Has liver cirrhosis
- 275 17. Has any other condition that, in the opinion of the investigator, excludes the patient from  
276 participating in this study  
277

278 **Vulnerable Populations**

279 No vulnerable populations are included in the research study.  
280

281 **Populations Vulnerable to Undue Influence or Coercion**

282 We are not specifically targeting any vulnerable populations.  
283

284 **Subject Recruitment**

285 900 potentially eligible subjects will be identified via a data abstraction by Penn Data Store using a data  
286 query algorithm that identifies patients who meet the inclusion criteria. Chart review will be conducted  
287 to source 423 eligible participants from this pool of subjects.  
288

289 **Subject Compensation**

290 Participants will not be financially compensated for their participation.  
291

292 **Procedures**

293 Screening - Phase 1: We will submit a data request of patients from the CCA practices of University  
294 City and Valley Forge from the Penn DataStore, based on an EMR algorithm that determines guideline-  
295 concordant colorectal cancer screening within PennChart. We estimate approximately 900 screen-  
296 eligible

297 patients will be identified through this EMR query, 423 of whom will be enrolled and randomized into  
298 the three arms. We anticipate conducting chart reviews for two months. During these chart reviews, the  
299 Research Assistants and the Research Coordinator will review the electronic medical record charts in  
300 PennChart (EPIC) to review each of the eligible patients pulled from Penn Data Store  
301 to confirm study eligibility.

302  
303 Randomization - Phase 2: Subjects will be randomly assigned Study ID numbers and then randomized  
304 with stratification to one of three arms using a computer-generated randomization algorithm. The  
305 research coordinator will record the randomization assignments on a master list which will be  
306 maintained by the research coordinator on a password protected computer in a locked office. The  
307 research coordinator and research assistants will assemble the mailings based on this master list.

308  
309 Outreach & Follow-up - Phase 3: Initial outreach letters will be sent to subjects. In the control arm the  
310 outreach will include a phone number to the VIP colonoscopy scheduling center. For the sequential  
311 choice arm, subjects will receive the same message as those in the control arm, indicating they are  
312 overdue for screening and including a phone number to the VIP screening scheduling center. For the  
313 active choice arm, subjects will receive both a mailed FIT kit and the option to call and schedule  
314 colonoscopy at the same time. After four weeks, a reminder letter will be sent to all subjects in all three  
315 arms who did not either schedule a colonoscopy appointment or complete and return a FIT kit. Subjects  
316 in the Control arm will receive a reminder letter that includes the same phone number to schedule  
317 colonoscopy. Subjects in the sequential choice arm will receive a second letter containing the phone  
318 number to the VIP screening scheduling center as well as a FIT kit. The active choice arm will receive a  
319 reminder that includes both the phone number to the VIP screening scheduling center and a reminder  
320 that they may alternatively complete the FIT that was initially mailed. The Research Coordinator and  
321 Research Assistants will be responsible for assembling the mailings. FIT kits will include a tube in which  
322 to deposit the stool sample, directions on how to collect and mail the sample, a letter about CRC  
323 screening, a lab requisition form, and a pre-paid return envelope.

324  
325 Sub-sample Questionnaire - Phase 5:  
326 A random subsample of 90 subjects will be selected to complete a questionnaire at least 4 months after  
327 they received the mailing. Through this questionnaire, the subjects will be asked to confirm their  
328 eligibility (e.g. that they had not had CRC screening within the USPSTF CRC screening guidelines)  
329 and provide additional demographic and socioeconomic status information as well as qualitative  
330 experience with the outreach materials and approach so that we can better understand what  
331 populations,  
332 if any, may be more likely impacted by different types of outreach modalities when engaging in CRC  
333 screening. We anticipate these questionnaires to take 10 minutes to complete over the phone. The  
334 research staff will make no more than three attempts to speak directly with the subject.

## 335 336 **Analysis Plan**

### 337 1.1 Power and Sample Size

338 Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data  
339 Store. Through other projects in primary care practices at Penn Medicine we found the accuracy rate of  
340 the EMR algorithm to be approximately 75%. As such, we anticipate we will have enough patients to  
341 enroll 423 subjects (and randomize 141 into each arm). We estimate a base return rate for the  
342 colonoscopy only (control) arm to be 5%, and we will consider a meaningful increase in response rate to  
343 be 10 percentage points for both the sequential choice and active choice arms as compared to control.

344 This will be sufficient sample size to detect a 10 percentage point increase in response rate using a two-  
345 tailed chi-square test with 80% power and a 5% level of significance.

346  
347 1.2 Data analysis

348 The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial  
349 outreach. We will conduct a chi-square analysis using Stata to compare arms 2 and 3 to arm 1 separately  
350 using intent-to-treat protocol. We will also compare arms 2 and 3 as a secondary analysis. We will  
351 quantitatively analyze the choice of screening test and evaluate the survey results by study arm. As  
352 exploratory analyses, we will evaluate response by practice location, age, gender, race/ethnicity, and  
353 income at the level of zip code.

354  
355 Analysis will be conducted by blinded members of the research team at least four months after the last  
356 FIT is mailed.

357  
358 **Data Confidentiality**

359 Paper-based records will be kept in a secure location and only be accessible to personnel involved in the  
360 study. Computer-based files will only be made available to personnel involved in the study through the  
361 use of access privileges and passwords. Prior to access to any study- related information, personnel will  
362 be required to sign statements agreeing to protect the security and confidentiality of identifiable  
363 information. Wherever feasible, identifiers will be removed from study-related information. Precautions  
364 are in place to ensure the data is secure by using passwords and encryption, because the research  
365 involves web-based surveys.

366  
367 **Subject Confidentiality**

368 Information about study subjects will be kept confidential and managed according to the requirements  
369 of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All PHI will be  
370 maintained on UPHS servers. Source documents are maintained in PennChart. No source documents  
371 will be printed or maintained in paper form at the study site. Data from PennChart will be recorded in  
372 Penn Medicine's REDCap system. The investigator and study team (which includes the research  
373 coordinator, and research assistants) will have access to PHI within PennChart and REDCap. We will  
374 label all PHI within REDCap as identifiable information so that de-identified exports are possible. All  
375 reports that include identifiable information will be stored on the Innovation Center secure drive,  
376 maintained behind the UPHS firewall. Once data analysis and manuscripts have been published, the  
377 databases will be removed from REDCap and the data will be de-identified on the secure drive. This  
378 deidentified dataset will be stored for up to five years after analysis is complete and manuscripts have  
379 been published. Once analysis is completed and any manuscripts are published, we will retain PHI no  
380 longer than seven years in accordance with government regulations, applicable policies, and  
381 institutional requirements.

382  
383 **Database Security/Protection Against Risk**

384 To assure that patient, physician and other informant confidentiality is preserved, individual identifiers  
385 (such as name and medical record number/physician billing identifier) are stored in a single password  
386 protected system that is accessible only to study research, analysis and IT staff. This system is hosted on  
387 site at The University of Pennsylvania (UPenn) and is protected by a secure firewall. Once a participant is  
388 in this system, they will be given a unique study identification number (ID). Any datasets and computer

389 files that leave the firewall will be stripped of all identifiers and individuals will be referred to by their  
390 study ID. The study ID will also be used on all analytical files.

391 The initial patient information collected for screening and recruitment will consist of name, address,  
392 phone number, dates, medical records numbers and health plan account numbers. This information will  
393 come from Electronic Chart reviews.  
394

#### 395 **Sensitive Research Information**

396 This Research does not involve collection of sensitive information about the subjects that should be  
397 excluded from the electronic medical record.

#### 398 399 **Subject Privacy**

400 We will only interact with the subsample of subjects with which we plan to call to conduct a follow-up  
401 questionnaire. With these subjects, we will conduct phone calls in a private area. When we call subjects,  
402 we will confirm the identify before administering the questionnaire. We will not be interacting with  
403 subjects in person.

#### 404 **Data Disclosure**

405 FIT test results will be disclosed to the subject's primary care physician for continuity of care.

#### 406 407 **Protected Health Information/Data Protection**

- 408 • Name
  - 409 • Street address, city, county, precinct, zip code, and equivalent geocodes
  - 410 • All elements of dates (except year) for dates directly related to an individual and all ages over 89
  - 411 • Telephone and fax numbers
  - 412 • Electronic mail addresses
  - 413 • Medical record numbers
  - 414 • Health Plan ID numbers
- 415

#### 416 **Consent Process**

##### 417 1.1 Overview

418 Waiver of consent for the main portion of this pilot study is being requested, as this study involves no  
419 more than minimal risk to subjects. Please see below. Verbal consent will be obtained from the  
420 subsample with whom we plan to conduct post intervention interviews (see script).  
421

##### 422 1.2 Children and Adolescents

423 Not applicable

##### 424 1.3 Adult Subjects Not Competent to Give Consent

425 Waiver of consent is being requested.

426  
427

#### 428 **Waiver of Consent**

429 1.1 Minimal Risk

430 This study involves no more than minimal risk to subjects. Colonoscopy and FIT are clinically available  
431 and utilized tests used to screen for colorectal cancer. The outreach methods in the three arms are all  
432 offered during routine clinical care either at Penn Medicine or other health systems across the country.  
433 The only research related activity is the randomization of subjects to different outreach strategies that  
434 would typically occur in practice.

435

436 1.2 Impact on Subjects Rights and Welfare

437 Subjects rights and welfare will not be adversely affected by the waiver of authorization and consent.  
438 All subjects will have the opportunity to voluntarily participate in CRC screening. Arm 1 (Colonoscopy  
439 only) will receive screening by colonoscopy if they elect. Arm 2 (Sequential Choice) will receive CRC  
440 screening either by Colonoscopy or FIT if they elect. Arm 3 (Active Choice) will receive CRC  
441 screening either by Colonoscopy or FIT if they elect. Each arm has the opportunity to engage in CRC  
442 screening through routine care as well.

443

444 1.3 Waiver Essential to Research

445 We believe that we would not be able to practically conduct the research without waiver of consent. If  
446 we had to obtain either written or verbal consent ahead of time, it would substantially limit our study  
447 population and it may alter their participation in the intervention. Thus, we would only learn about the  
448 response rate for patients who we were able to speak to for consent. This, would limit the  
449 generalizability to practice. Obtaining waiver of consent would allow us to avoid the potential  
450 selection/volunteer bias for inclusion of patients particularly interested in screening that can occur when  
451 consent is required. Since our main objective is to understand the potential influence varying outreach  
452 strategies on subject behavior, we believe that obtaining consent would compromise our primary  
453 objective. Additionally, we have received waiver of consent for similar studies related to colorectal  
454 cancer screening outreach.

455

456 1.4 Additional Information to Subjects

457 Subjects will receive information about the risks and benefits of FIT through our outreach and about the  
458 risk and benefits of colonoscopy from the physician performing the procedure.

459

460

461 1.5 Written Statement of Research

462 No statement of research will be provided.

463

464 **Potential Study Risks**

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

472

473 **Potential Study Benefits**

474 If a participant completes colonoscopy or completes and returns the FIT, both of which are standard  
475 clinical care, the subjects will potentially benefit from participation by increasing the chances of

476 identifying colorectal cancer at an early stage. Information learned from this study may benefit society  
477 through a better understanding of how to effectively increase overall participation rates in CRC  
478 screening which could in turn reduce the rate of CRC mortality.

479

480 **Data and Safety Monitoring**

481 Safety will be monitored on an ongoing basis by the PI and the study team. The PI or designee will  
482 review the study charts to evaluate events at each subject interaction to ensure the grade, relationship  
483 to the study procedure, expectedness and the course of action for each subject is documented.

484

485 **Risk/Benefit Assessment**

486 The risks associated with this study are no more than minimal. Better knowledge of how to increase  
487 mailed screening could potentially address one of the major barriers of accessing care, i.e. having  
488 patients come in for clinical office visits. Additionally, FIT is less invasive than colonoscopy and, according  
489 to the USPSTF, considered equally effective if conducted once a year (as opposed to having a  
490 colonoscopy once every ten years). For these reasons and those outlined in the above benefits section,  
491 the Principal Investigator believes that the risks of participating in the study are outweighed by the  
492 potential benefits of participating in the study.

493

## 494 Final Protocol

495

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

498

### 499 Abstract

500 A 3-arm randomized trial assessing whether the rate of completion of colorectal cancer screening  
501 is increased when patients receive a sequential choice in screening options (colonoscopy followed  
502 by Fecal Immunochemical Testing (FIT)) or an active choice (FIT or colonoscopy offered  
503 together) versus colonoscopy alone. The targeted population is patients within the University City  
504 and Valley Forge Community Care Associates (CCA) practices at the University of Pennsylvania  
505 Health System.

506

### 507 Study Instruments

508 The primary endpoint being evaluated is the rate of participation in colorectal cancer screening between  
509 the two intervention arms (Sequential Choice, Active Choice) versus the control arm (colonoscopy only).  
510 The FIT is a well validated tool for colorectal cancer screening and is one of the screening modalities  
511 recommended by the USPSTF. The control arm will be sent a letter inviting them to schedule screening  
512 colonoscopy directly through the Gastroenterology Call Center. If not scheduled within 4 weeks, subjects  
513 will receive a mailed reminder to call to schedule. The Sequential Choice arm will be sent the same initial  
514 outreach as the control arm. If not scheduled within 4 weeks, subjects will receive a mailed reminder  
515 including the call center number as well as the option to complete a FIT kit mailed along with the  
516 reminder. The Active Choice arm of the study will be sent a letter offering the choice of Colonoscopy or  
517 completion of the FIT kit included with the initial mailing. If subjects in this group have not either  
518 scheduled colonoscopy nor completed FIT within 4 weeks, they will receive a mailed reminder to call to  
519 schedule colonoscopy or to complete the original mailed FIT.

520

521 A sub-sample of 90 subjects will be called to complete a questionnaire over the phone ~~4~~**beginning**  
522 **approximately 6** months after initial outreach was mailed. ~~The subjects will be asked to confirm their~~  
523 ~~eligibility (e.g. that they had not had CRC screening within the USPSTF CRC screening guidelines) and~~  
524 ~~provide additional demographic and socioeconomic information so that we can better understand what~~  
525 ~~populations, if any, may have differential response rates. We will also ask them~~ **The subjects will be**  
526 **asked to explain their experience with CRC screening prior to our initial outreach (November 2017), as**  
527 **well as** about their perception of the impact and design of CRC screening outreach. **Additional**  
528 **questions will probe for potential barriers to screening participation and ways to improve**  
529 **participation in the future.** ~~Demographic and socioeconomic questions are modified from demographic~~  
530 ~~questions on the Behavioral Risk Factor Surveillance System survey, administered by the Centers for~~  
531 ~~Disease Control and Prevention. See attached sub-sample questionnaire.~~

532

### 533 Group Modifications

534 For subjects in the Control (Colonoscopy only) arm of the study, the post outreach phone questionnaires  
535 will not include questions regarding mailed FIT.

536

537

538

539

540 **Method for Assigning Subjects to Groups**

541 Subjects will be randomly assigned Study ID numbers and then randomized to one of three study arms  
542 stratified by the two practice locations (University City and Valley Forge) using a computer-generated  
543 randomization algorithm. The research coordinator will record the randomization assignments on a  
544 master list which will be maintained by the research coordinator on a password protected computer in a  
545 locked office. The research coordinator and research assistants will assemble the mailings based on this  
546 master list.

547

548

549 **Administration of Surveys and/or Process**

550 90 subjects will be randomly selected for the questionnaire. We anticipate the post outreach  
551 questionnaires to take 10 minutes to complete over the phone. The research staff will make no more  
552 than three attempts to speak directly with the subject. Based on a previous project where we reached  
553 about 50% of patients via phone call, we anticipate reaching approximately 45 subjects (15 in each  
554 arm) to complete this sub-sample questionnaire.

555

556 **Administration of Surveys**

557 All subjects will complete a baseline and post-intervention survey. The baseline survey will collect basic  
558 demographics and baseline medication adherence and blood pressure monitoring frequency and be  
559 conducted over the phone after the participant has been consented. The post-intervention survey will  
560 collect similar adherence and monitoring information, as well as qualitative data regarding patient  
561 perceptions about the interventions. The post-intervention survey will be completed at the in-person 4  
562 month visit. These surveys should take no more than 15 minutes to complete. Demographic and socio-  
563 economic questions are modified from demographic questions on the Behavioral Risk Factor  
564 Surveillance System survey, administered by the Centers for Disease Control and Prevention.

565

566 **Objectives**

567 1.4 Objectives

568 The specific aim of this study is to assess the effectiveness of two different mailed outreach activities  
569 (sequential choice of colonoscopy then FIT, active choice of colonoscopy and FIT) versus colonoscopy  
570 only in increasing participation in CRC screening.

571

572 1.5 Primary Outcome Variable

573 The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial  
574 outreach

575

576 1.6 Secondary Outcome Variable(s)

577 The secondary outcome is the choice of screening test between FIT and colonoscopy.

578

579 Additional outcomes include demographic and socioeconomic characteristics of subjects who  
580 participate, as well as exploratory qualitative data regarding experience with the different outreach  
581 methodologies. Additional outcome is the percentage of FIT screening results that are positive,  
582 percentage of those positive FIT tests that receive follow-up diagnostic colonoscopy, and percentage of  
583 colonoscopies that find adenomas, advanced adenomas, and cancer.

584

585 **Background**

586 1.1 Program Goals

587 Despite effective strategies for prevention, early detection, and treatment, colorectal cancer (CRC) is the  
588 third most common type of cancer and second leading cause of cancer death in the United States. The  
589 US Preventive Services Task Force (USPSTF) recommends routine CRC screening for all individuals  
590 aged 50-75; yet, despite aggressive public health efforts to promote screening, national rates are still  
591 suboptimal at 59-64%.

592

593 Colonoscopy is the predominant form of screening in this country due to perceived effectiveness by  
594 providers, but it entails a significant cost in time, resources, and perceived discomfort. The fecal  
595 immunochemical test (FIT) is an attractive screening option as it is less invasive than traditional lower  
596 endoscopy and can be mailed to patients to complete at home. A recent study has shown that offering  
597 the choice of colonoscopy or stool-based testing in a clinic setting increases screening rates, but receipt  
598 of colonoscopy has better durability since stool-based testing has to occur every year.

599

600 In this study, we will be using population-based outreach screening to evaluate the feasibility of a  
601 proactive screening program to promote fecal immunochemical testing (FIT) and/or colonoscopy  
602 through mailed outreach by leveraging principles of behavioral economics. We know that mailed FIT  
603 outreach circumvents the need for an office visit and eliminates friction in the screening process, since  
604 patients can perform testing at home in minutes, but it is not clear how patients may respond to  
605 different choice architecture about FIT versus colonoscopy as they have historically been seen as  
606 competing, rather than complementary strategies. Behavioral economics suggests that choice  
607 architecture may also impact response based on how the intervention is designed. For example, offering  
608 the choice of colonoscopy with the mailed FIT kit may enhance participation (as compared to offering  
609 colonoscopy alone) since it makes the decision an active choice, where the patient is choosing between  
610 two options as opposed to the traditional opt-in approach. Offering mailed FIT after colonoscopy, as is  
611 currently the standard during in-office visits, may also increase participation. By evaluating the  
612 effectiveness of these alternative choice approaches, we will enhance the public health capacity and  
613 efficiency to increase CRC screening uptake and reduce preventable death from this disease.

614

615 **Statistical Considerations**

616 1.1 Power and sample size

617 Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data  
618 Store. Through other projects in primary care practices at Penn Medicine we found the accuracy rate of  
619 the EMR algorithm to be approximately 75%. As such, we anticipate we will have enough patients to  
620 enroll 423 subjects (and randomize 141 into each arm). We estimate a base return rate for the  
621 colonoscopy only (control) arm to be 5%, and we will consider a meaningful increase in response rate to  
622 be ~~10~~ **11** percentage points for both the sequential choice and active choice arms as compared to  
623 control. This will be sufficient sample size to detect a ~~10~~ **11** percentage point increase in response rate  
624 using a two-tailed chi-square test with 80% power and a ~~5% level of significance~~. Type I error rate of  
625 .025, accounting for two pairwise comparisons with Bonferroni correction ( $.05/2 = .025$ ).

626

627 1.2 Data analysis

628 The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial  
629 outreach. We will conduct a chi-square analysis using Stata to compare arms 2 and 3 to arm 1 separately  
630 using intent-to-treat protocol. We will also compare arms 2 and 3 as a secondary analysis. We will

631 quantitatively analyze the choice of screening test and evaluate the survey results by study arm. As  
632 exploratory analyses, we will evaluate response by practice location, age, gender, race/ethnicity, and  
633 income at the level of zip code.

634  
635 Analysis will be conducted by blinded members of the research team at least four months after the last  
636 FIT is mailed.

637

## 638 **Study Design**

### 639 1.1 Design

640 Randomized: Subjects will be randomly assigned Study ID numbers and then randomized to one of  
641 three study arms stratified by practice location using a computer-generated randomization algorithm.  
642 The research coordinator will record the randomization assignments on a master list which will be  
643 maintained on a password protected computer in a locked office. The research coordinator and research  
644 assistants will assemble the mailings based on this master list.

645

646 Blinding: The investigators will be blinded to the randomization assignment. The research coordinator  
647 and research assistants will be unblinded. The blind may be broken for clinical care purposes.

648

### 649 1.2 Consent Process

650 Waiver of consent for the main portion of this pilot study is being requested, as this study involves no  
651 more than minimal risk to subjects. Colonoscopy and FIT are clinically available and utilized tests used to  
652 screen for colorectal cancer. The outreach methods in the three arms are all offered during routine  
653 clinical care either at Penn Medicine or other health systems across the country. The only research  
654 related activity is the randomization of subjects to different outreach strategies that would typically  
655 occur in practice. Subjects will receive information about the risks and benefits of FIT through our  
656 outreach and about the  
657 risk and benefits of colonoscopy from the physician performing the procedure.

658

659 Subjects rights and welfare will not be adversely affected by the waiver of authorization and consent.  
660 All subjects will have the opportunity to voluntarily participate in CRC screening. Arm 1 (Colonoscopy  
661 only) will receive screening by colonoscopy if they elect. Arm 2 (Sequential Choice) will receive CRC  
662 screening either by Colonoscopy or FIT if they elect. Arm 3 (Active Choice) will receive CRC  
663 screening either by Colonoscopy or FIT if they elect. Each arm has the opportunity to engage in CRC  
664 screening through routine care as well.

665

666 We believe that we would not be able to practically conduct the research without waiver of consent. If  
667 we had to obtain either written or verbal consent ahead of time, it would substantially limit our study  
668 population and it may alter their participation in the intervention. Thus, we would only learn about the  
669 response rate for patients who we were able to speak to for consent. This, would limit the  
670 generalizability to practice. Obtaining waiver of consent would allow us to avoid the potential  
671 selection/volunteer bias for inclusion of patients particularly interested in screening that can occur when  
672 consent is required. Since our main objective is to understand the potential influence varying outreach  
673 strategies on subject behavior, we believe that obtaining consent would compromise our primary  
674 objective. Additionally, we have received waiver of consent for similar studies related to colorectal  
675 cancer screening outreach.

676

677 Verbal consent will be obtained from the subsample with whom we plan to conduct post intervention  
678 interviews (see script).

679

### 680 **Study Duration**

681 We anticipate conducting chart reviews for two months, mailed outreach and reminder follow-up for  
682 two months, waiting for completion of screening for an additional 4 months, and sub sample interview,  
683 data analysis and manuscript compilation for 4 months. Thus, we anticipate this pilot project to last 12  
684 months. Project date of the proposed study: July 1, 2017 - June 30, 2018.

685

### 686 **Resources Necessary for Human Research Protections**

687 Shivan Mehta is the PI of this study. He is a gastroenterologist and assistant professor of medicine at the  
688 Perelman School of Medicine. All members of the research team have completed CITI human subjects  
689 research training. The Research Coordinator will provide thorough education and training to the  
690 Research Assistants to ensure that they are well-prepared to carry out the duties in their job  
691 descriptions. Additionally, the Research Coordinator will audit 10% of the electronic medical record  
692 reviews that the Research Assistants complete, in order to check for compliance. Detailed Standard  
693 Operating Procedure documents for the project will be accessible to all members of the research team,  
694 which will keep research staff informed about the protocol and their related duties. There are adequate  
695 facilities to conduct the research; all research staff have adequate office space on the UPenn campus.

696

### 697 **Target Population**

698 Eligibility Criteria: The study population includes patients between 50 to 74 years old who have received  
699 care at the University City and Valley Forge CCA practices, are due for screening, and are asymptomatic  
700 for CRC.

701

### 702 **Subjects Enrolled by Penn Researchers**

703 423

704

### 705 **Subjects Enrolled by Collaborating Researchers**

706 0

707

### 708 **Accrual**

709 Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data  
710 Store. Through other projects in primary care practices at Penn Medicine we found the accuracy rate of  
711 the EMR algorithm to be approximately 75%. As such, we anticipate we will have enough patients to  
712 enroll 423 subjects (and randomize 141 into each arm). We estimate a base return rate for the  
713 colonoscopy only (control) arm to be 5%, and we will consider a meaningful increase in response rate  
714 to be 10 percentage points for both the sequential choice and active choice arms as compared to  
715 control.

716 This will be sufficient sample size to detect a 10 percentage point increase in response rate using a two-  
717 tailed chi-square test with 80% power and a 5% level of significance.

718

719

720

721

722

723 **Key Inclusion Criteria**

- 724 1. Between 50 and 74 years old  
725 2. Has had at least two office visits at the University City or Valley Forge CCA practice within the past 2  
726 years (at time of chart review)  
727 3. Due for colorectal cancer (CRC) screening  
728 4. Asymptomatic for CRC  
729 5. Zip code listed in PennChart as part of the subjects address is within the Philadelphia-Wilmington-  
730 Camden Metropolitan Statistical Area  
731 6. Has a primary care provider who is a University City or valley Forge Family Medicine provider  
732

733 **Key Exclusion Criteria**

- 734 1. Has had prior colonoscopy within 10 years, sigmoidoscopy within 5 years, and FOBT/FIT within twelve  
735 months of the chart review (We will exclude patients who self-report undergoing any of the above  
736 procedures)  
737 2. Has a history of CRC  
738 3. Has a history of other GI cancer  
739 4. Has history of confirmed Inflammatory Bowel Disease (IBD) (e.g. Crohns disease, ulcerative colitis)  
740 Irritable bowel syndrome does not exclude patients.  
741 5. Has history of colitis other than Crohns disease or ulcerative colitis  
742 6. Has had a colectomy  
743 7. Has a relative that has been diagnosed with CRC  
744 8. Has been diagnosed with Lynch Syndrome (i.e. HNPCC)  
745 9. Has been diagnosed with Familial Adenomatous Polyposis (FAP)  
746 10. Has iron deficiency anemia  
747 11. Has history of lower GI bleeding  
748 12. Has metastatic (Stage IV) blood or solid tumor cancer  
749 13. Has end stage renal disease  
750 14. Has had congestive heart failure  
751 15. Has dementia  
752 16. Has liver cirrhosis  
753 17. Has any other condition that, in the opinion of the investigator, excludes the patient from  
754 participating in this study  
755

756 **Vulnerable Populations**

757 No vulnerable populations are included in the research study.  
758

759 **Populations Vulnerable to Undue Influence or Coercion**

760 We are not specifically targeting any vulnerable populations.  
761

762 **Subject Recruitment**

763 900 potentially eligible subjects will be identified via a data abstraction by Penn Data Store using a data  
764 query algorithm that identifies patients who meet the inclusion criteria. Chart review will be conducted

765 to source 423 eligible participants from this pool of subjects.

766

### 767 **Subject Compensation**

768 Participants will not be financially compensated for their participation.

769

### 770 **Procedures**

771 Screening - Phase 1: We will submit a data request of patients from the CCA practices of University  
772 City and Valley Forge from the Penn DataStore, based on an EMR algorithm that determines guideline-  
773 concordant colorectal cancer screening within PennChart. We estimate approximately 900 screen-  
774 eligible

775 patients will be identified through this EMR query, 423 of whom will be enrolled and randomized into  
776 the three arms. We anticipate conducting chart reviews for two months. During these chart reviews, the  
777 Research Assistants and the Research Coordinator will review the electronic medical record charts in  
778 PennChart (EPIC) to review each of the eligible patients pulled from Penn Data Store  
779 to confirm study eligibility.

780

781 Randomization - Phase 2: Subjects will be randomly assigned Study ID numbers and then randomized  
782 with stratification to one of three arms using a computer-generated randomization algorithm. The  
783 research coordinator will record the randomization assignments on a master list which will be  
784 maintained by the research coordinator on a password protected computer in a locked office. The  
785 research coordinator and research assistants will assemble the mailings based on this master list.

786

787 Outreach & Follow-up - Phase 3: Initial outreach letters will be sent to subjects. In the control arm the  
788 outreach will include a phone number to the VIP colonoscopy scheduling center. For the sequential  
789 choice arm, subjects will receive the same message as those in the control arm, indicating they are  
790 overdue for screening and including a phone number to the VIP screening scheduling center. For the  
791 active choice arm, subjects will receive both a mailed FIT kit and the option to call and schedule  
792 colonoscopy at the same time. After four weeks, a reminder letter will be sent to all subjects in all three  
793 arms who did not either schedule a colonoscopy appointment or complete and return a FIT kit. Subjects  
794 in the Control arm will receive a reminder letter that includes the same phone number to schedule  
795 colonoscopy. Subjects in the sequential choice arm will receive a second letter containing the phone  
796 number to the VIP screening scheduling center as well as a FIT kit. The active choice arm will receive a  
797 reminder that includes both the phone number to the VIP screening scheduling center and a reminder  
798 that they may alternatively complete the FIT that was initially mailed. The Research Coordinator and  
799 Research Assistants will be responsible for assembling the mailings. FIT kits will include a tube in which  
800 to deposit the stool sample, directions on how to collect and mail the sample, a letter about CRC  
801 screening, a lab requisition form, and a pre-paid return envelope.

802

803 Sub-sample Questionnaire - Phase 5:

804 A random subsample of 90 subjects will be selected to complete a questionnaire at least 4  
805 **approximately 6 months** after they received the mailing. Through this questionnaire, ~~the subjects will~~  
806 **be asked to explain their experience with CRC screening outreach. Additional questions will probe for**  
807 **potential barriers to screening participation, and ways to improve participation in the future.** ~~confirm~~  
808 ~~their eligibility (e.g. that they had not had CRC screening within the USPSTF CRC screening guidelines)~~  
809 ~~and provide additional demographic and socioeconomic status information as well as qualitative~~  
810 ~~experience with the outreach materials and approach so that we can better understand what~~

811 populations, if any, may be more likely impacted by different types of outreach modalities when  
812 engaging in CRC screening. We anticipate these questionnaires to take 10 minutes to complete over the  
813 phone. The research staff will make no more than three attempts to speak directly with the subject.  
814

815

## 816 **Analysis Plan**

### 817 1.1 Power and Sample Size

818 Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data  
819 Store. Through other projects in primary care practices at Penn Medicine we found the accuracy rate of  
820 the EMR algorithm to be approximately 75%. As such, we anticipate we will have enough patients to  
821 enroll 423 subjects (and randomize 141 into each arm). We estimate a base return rate for the  
822 colonoscopy only (control) arm to be 5%, and we will consider a meaningful increase in response rate to  
823 be ~~10~~ **11** percentage points for both the sequential choice and active choice arms as compared to  
824 control. This will be sufficient sample size to detect a ~~10~~ **11** percentage point increase in response rate  
825 using a two-tailed chi-square test with 80% power and a **Type 1 error rate of .025, accounting for two**  
826 **pairwise comparisons with Bonferroni correction (.05/2 = .025).** ~~5% level of significance.~~  
827

827

### 828 1.2 Data analysis

829 The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial  
830 outreach. We will conduct a chi-square analysis using Stata to compare arms 2 and 3 to arm 1 separately  
831 using intent-to-treat protocol. We will also compare arms 2 and 3 as a secondary analysis. We will  
832 quantitatively analyze the choice of screening test and evaluate the survey results by study arm. As  
833 exploratory analyses, we will evaluate response by practice location, age, gender, race/ethnicity, and  
834 income at the level of zip code.  
835

835

836 Analysis will be conducted by blinded members of the research team at least four months after the last  
837 FIT is mailed.

837

838

## 839 **Data Confidentiality**

840 Paper-based records will be kept in a secure location and only be accessible to personnel involved in the  
841 study. Computer-based files will only be made available to personnel involved in the study through the  
842 use of access privileges and passwords. Prior to access to any study- related information, personnel will  
843 be required to sign statements agreeing to protect the security and confidentiality of identifiable  
844 information. Wherever feasible, identifiers will be removed from study-related information. Precautions  
845 are in place to ensure the data is secure by using passwords and encryption, because the research  
846 involves web-based surveys.  
847

847

## 848 **Subject Confidentiality**

849 Information about study subjects will be kept confidential and managed according to the requirements  
850 of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All PHI will be  
851 maintained on UPHS servers. Source documents are maintained in PennChart. No source documents  
852 will be printed or maintained in paper form at the study site. Data from PennChart will be recorded in  
853 Penn Medicine's REDCap system. The investigator and study team (which includes the research  
854 coordinator, and research assistants) will have access to PHI within PennChart and REDCap. We will  
855 label all PHI within REDCap as identifiable information so that de-identified exports are possible. All  
856 reports that include identifiable information will be stored on the Innovation Center secure drive,

857 maintained behind the UPHS firewall. Once data analysis and manuscripts have been published, the  
858 databases will be removed from REDCap and the data will be de-identified on the secure drive. This  
859 deidentified dataset will be stored for up to five years after analysis is complete and manuscripts have  
860 been published. Once analysis is completed and any manuscripts are published, we will retain PHI no  
861 longer than seven years in accordance with government regulations, applicable policies, and  
862 institutional requirements.

863

#### 864 **Database Security/Protection Against Risk**

865 To assure that patient, physician and other informant confidentiality is preserved, individual identifiers  
866 (such as name and medical record number/physician billing identifier) are stored in a single password  
867 protected system that is accessible only to study research, analysis and IT staff. This system is hosted on  
868 site at The University of Pennsylvania (UPenn) and is protected by a secure firewall. Once a participant is  
869 in this system, they will be given a unique study identification number (ID). Any datasets and computer  
870 files that leave the firewall will be stripped of all identifiers and individuals will be referred to by their  
871 study ID. The study ID will also be used on all analytical files.

872 The initial patient information collected for screening and recruitment will consist of name, address,  
873 phone number, dates, medical records numbers and health plan account numbers. This information will  
874 come from Electronic Chart reviews.

875

#### 876 **Sensitive Research Information**

877 This Research does not involve collection of sensitive information about the subjects that should be  
878 excluded from the electronic medical record.

879

#### 880 **Subject Privacy**

881 We will only interact with the subsample of subjects with which we plan to call to conduct a follow-up  
882 questionnaire. With these subjects, we will conduct phone calls in a private area. When we call subjects,  
883 we will confirm the identify before administering the questionnaire. We will not be interacting with  
884 subjects in person.

#### 885 **Data Disclosure**

886 FIT test results will be disclosed to the subject's primary care physician for continuity of care.

887

#### 888 **Protected Health Information/Data Protection**

- 889 • Name
- 890 • Street address, city, county, precinct, zip code, and equivalent geocodes
- 891 • All elements of dates (except year) for dates directly related to an individual and all ages over 89
- 892 • Telephone and fax numbers
- 893 • Electronic mail addresses
- 894 • Medical record numbers
- 895 • Health Plan ID numbers

896

897

898 **Consent Process**

899 1.1 Overview

900 Waiver of consent for the main portion of this pilot study is being requested, as this study involves no  
901 more than minimal risk to subjects. Please see below. Verbal consent will be obtained from the  
902 subsample with whom we plan to conduct post intervention interviews (see script).

903

904 1.2 Children and Adolescents

905 Not applicable

906 1.3 Adult Subjects Not Competent to Give Consent

907 Waiver of consent is being requested.

908

909 **Waiver of Consent**

910 1.1 Minimal Risk

911 This study involves no more than minimal risk to subjects. Colonoscopy and FIT are clinically available  
912 and utilized tests used to screen for colorectal cancer. The outreach methods in the three arms are all  
913 offered during routine clinical care either at Penn Medicine or other health systems across the country.  
914 The only research related activity is the randomization of subjects to different outreach strategies that  
915 would typically occur in practice.

916

917 1.2 Impact on Subjects Rights and Welfare

918 Subjects rights and welfare will not be adversely affected by the waiver of authorization and consent.  
919 All subjects will have the opportunity to voluntarily participate in CRC screening. Arm 1 (Colonoscopy  
920 only) will receive screening by colonoscopy if they elect. Arm 2 (Sequential Choice) will receive CRC  
921 screening either by Colonoscopy or FIT if they elect. Arm 3 (Active Choice) will receive CRC  
922 screening either by Colonoscopy or FIT if they elect. Each arm has the opportunity to engage in CRC  
923 screening through routine care as well.

924

925 1.3 Waiver Essential to Research

926 We believe that we would not be able to practically conduct the research without waiver of consent. If  
927 we had to obtain either written or verbal consent ahead of time, it would substantially limit our study  
928 population and it may alter their participation in the intervention. Thus, we would only learn about the  
929 response rate for patients who we were able to speak to for consent. This, would limit the  
930 generalizability to practice. Obtaining waiver of consent would allow us to avoid the potential  
931 selection/volunteer bias for inclusion of patients particularly interested in screening that can occur when  
932 consent is required. Since our main objective is to understand the potential influence varying outreach  
933 strategies on subject behavior, we believe that obtaining consent would compromise our primary  
934 objective. Additionally, we have received waiver of consent for similar studies related to colorectal  
935 cancer screening outreach.

936

937 1.4 Additional Information to Subjects

938 Subjects will receive information about the risks and benefits of FIT through our outreach and about the  
939 risk and benefits of colonoscopy from the physician performing the procedure.

940

941

942

943

944 1.5 Written Statement of Research

945 No statement of research will be provided.

946

947 **Potential Study Risks**

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

955

956 **Potential Study Benefits**

957 If a participant completes colonoscopy or completes and returns the FIT, both of which are standard  
958 clinical care, the subjects will potentially benefit from participation by increasing the chances of  
959 identifying colorectal cancer at an early stage. Information learned from this study may benefit society  
960 through a better understanding of how to effectively increase overall participation rates in CRC  
961 screening which could in turn reduce the rate of CRC mortality.

962

963 **Data and Safety Monitoring**

964 Safety will be monitored on an ongoing basis by the PI and the study team. The PI or designee will  
965 review the study charts to evaluate events at each subject interaction to ensure the grade, relationship  
966 to the study procedure, expectedness and the course of action for each subject is documented.

967

968 **Risk/Benefit Assessment**

969 The risks associated with this study are no more than minimal. Better knowledge of how to increase  
970 mailed screening could potentially address one of the major barriers of accessing care, i.e. having  
971 patients come in for clinical office visits. Additionally, FIT is less invasive than colonoscopy and, according  
972 to the USPSTF, considered equally effective if conducted once a year (as opposed to having a  
973 colonoscopy once every ten years). For these reasons and those outlined in the above benefits section,  
974 the Principal Investigator believes that the risks of participating in the study are outweighed by the  
975 potential benefits of participating in the study.

976

977  
978

## Summary of Protocol Changes Modifications LOG

979 **Protocol:** Choice Architecture and Colorectal Cancer Screening Outreach  
980 **University of Pennsylvania Principal Investigator:** Shivan Mehta, MD

981

Date of Submission	Description of Modification	Rationale for Modification	Approval date
06/28/2017	Initial submission		07/28/2017
09/06/2017	Updates to study personnel	Add Research Assistant: Induru Vikrant	09/13/2017
11/21/2017	Updates to study personnel	Add student Research Assistant: Hoyt Gong Remove student research assistant: Aaron Aahn	11/29/2017
02/06/2018	1) Updates to study personnel 2) Updated patient materials (questionnaire)	1) Remove student research assistant: Hoyt Gong 2) modified questionnaire to be more open ended, to gather more information and be more hypothesis generating than specific	02/12/2018
04/27/2018	1) Updated patient materials (questionnaire) 2) Updated study protocol (Phase 5: Sub-sample Questionnaire)	Revised the questionnaire to be more of a guided interview with open ended questions to gather a broader set of experiences, aimed at informing further research opportunities.	05/07/2018
05/16/2018	1) Updates to study personnel 2) Updated study protocol 3) Updated study protocol: analysis plan	1) Remove student research assistant: Tim McAuliffe; Remove study contact Rebecca Pepe; Add student research assistant: Humphrey Shen 2) Updated format to study protocol to reflect original and all modifications 3) Before beginning any analysis, we felt it necessary to revisit outcomes and provide a more detailed/thorough analysis plan to ensure both were as complete as possible.	05/16/2018
06/18/2018	1) Update study personnel 2) Continuing Review	1) Add student intern: David Santos	07/27/2018

982  
983

984 Initial Statistical Analysis Plan

985

986 **Analysis Plan**

987 1.1 Power and Sample Size

988 Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data Store.  
989 Through other projects in primary care practices at Penn Medicine we found the accuracy rate of the EMR  
990 algorithm to be approximately 75%. As such, we anticipate we will have enough patients to enroll 423 subjects  
991 (and randomize 141 into each arm). We estimate a base return rate for the colonoscopy only (control) arm to be  
992 5%, and we will consider a meaningful increase in response rate to be 10 percentage points for both the  
993 sequential choice and active choice arms as compared to control. This will be sufficient sample size to detect a  
994 10 percentage point increase in response rate using a two-tailed chi-square test with 80% power and a 5% level  
995 of significance.

996

997 1.2. Data Analysis

998 The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial outreach. We  
999 will conduct a chi-square analysis using Stata to compare arms 2 and 3 to arm 1 separately using intent-to-treat  
000 protocol. We will also compare arms 2 and 3 as a secondary analysis. We will quantitatively analyze the choice of  
001 screening test and evaluate the survey results by study arm. As exploratory analyses, we will evaluate response  
002 by practice location, age, gender, race/ethnicity, and income at the level of zip code.

003

004 Analysis will be conducted by blinded members of the research team at least four months after the last FIT is  
005 mailed.

006

007

## Final Statistical Analysis Plan

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

### Analysis Plan

#### 1.1 Power and Sample Size

Approximately 900 potentially eligible subjects will be identified via a data abstraction by Penn Data Store. Through other projects in primary care practices at Penn Medicine we found the accuracy rate of the EMR algorithm to be approximately 75%. As such, we anticipate we will have enough patients to enroll 423 subjects (and randomize 141 into each arm). We estimate a base return rate for the colonoscopy only (control) arm to be 5%, and we will consider a meaningful increase in response rate to be ~~10~~ **11** percentage points for both the sequential choice and active choice arms as compared to control. This will be sufficient sample size to detect a ~~10~~ **11** percentage point increase in response rate using a two-tailed chi-square test with 80% power and a Type 1 error rate of .025, accounting for two pairwise comparisons with Bonferroni correction ( $.05/2 = .025$ ). ~~5% level of significance.~~

#### 1.2. Data Analysis

The primary outcome is CRC screening completion (FIT or colonoscopy) within 4 months of initial outreach. We will conduct a chi-square analysis using Stata to compare arms 2 and 3 to arm 1 separately using intent-to-treat protocol. We will also compare arms 2 and 3 as a secondary analysis. We will quantitatively analyze the choice of screening test and evaluate the survey results by study arm. As exploratory analyses, we will evaluate response by practice location, age, gender, race/ethnicity, and income at the level of zip code.

Analysis will be conducted by blinded members of the research team at least four months after the last FIT is mailed.

## Summary of Statistical Analysis Plan Modifications

Before analysis, we felt it necessary to revisit outcomes and provide a more detailed/thorough analysis plan to ensure both were as complete as possible. The analysis plan was updated to be more descriptive of the specific comparisons that would be made, to include communication modality and demographics.

## Appendix A – Final Survey Instrument

We're calling from <Penn Medicine Pt's Practice> to ask you a few questions about screening for colon cancer. The questions shouldn't take more than 10-15 minutes to complete, and we value your input on this important subject. There are no wrong answers and your responses could help us better care for our patients in the future.

Do you have a few minutes now to answer a few questions?

**1) What have you heard about getting screened for colon cancer? Whether you've had experience with it firsthand or heard about it from someone else, anything you've heard is helpful to us.** (Probe for awareness of screening options, social influence, barriers, frequency, cost, ease, any past screening/non-screening experiences)

**2) Prior to November 2017, had you ever been screened for colon cancer before? Y/N**

If N: question 3

If Y: which test?

If Y: do you remember when?

If Y: do you remember where it was done?

**3) In November 2017, we mailed you an invitation to participate in colon cancer screening. What was your experience with that invitation?**

(if no recollection/didn't receive it, skip to question 5)

**4) Our records show that you didn't complete FIT/Colonoscopy after receiving that invitation. Don't worry – you're not alone, many people didn't! Can you tell me about how that invitation helped you think about getting yourself screened for colon cancer? What are some of the reasons you decided not to get it done? What would facilitate you getting screened in the future?**

or

Our records show that you completed FIT/Colonoscopy after receiving that invitation – that's fantastic! **Can you tell me about how that invitation helped you think about getting yourself screened for colon cancer? What are some of the reasons you decided to get it done?**

- a. Follow-up: **Good or bad, we'd love to hear your screening story so we can capitalize on our strengths and improve where we fall short. Can you tell us about this colon cancer screening experience?** (Convenience/ease, prep, time it took, confidence in process/results, repeat, what would you tell others about it?)

113 5) The FIT test is an at-home screening test for colon cancer where you send a swab of stool to the lab to  
114 test for blood. Most doctors want their patients who are 50-75 years old to either do this test once per  
115 year, or get a colonoscopy once every ten years. **In the future, would you prefer to have a colonoscopy**  
116 **every 10 years or take a FIT every year?**

- 117 a) FIT
- 118 b) Colonoscopy
- 119 c) No preference
- 120 d) Prefer not to be screened

121  
122 6) **Can you tell us more about why FIT/Colonoscopy is your preference?**

123  
124 7) **What would be the most helpful thing Penn Medicine could do to help ensure you get screened for**  
125 **colon cancer regularly?**

126  
127 **Thank you for taking the time to give us your input, we appreciate it!**

128 **If you have any questions about this call, the FIT kit, colonoscopy or colon cancer screening in general, please**  
129 **call us at XXX-XXX-XXXX or speak with your Doctor.**

146 Appendix B – Mailed Outreach Language  
147

148 **Initial Outreach**

149 **Colonoscopy Only**

150 Our records show that you may be overdue for your colon cancer screening  
151 Penn Medicine is offering a special VIP hotline to patients for scheduling screening colonoscopy.  
152 Please call XXX-XXX-XXXX to schedule your colonoscopy right away.  
153

154 Call the VIP hotline XXX-XXX-XXXX to schedule your screening colonoscopy today!  
155

156 **Sequential Choice**

157 Our records show that you may be overdue for your colon cancer screening  
158 Penn Medicine is offering a special VIP hotline to patients for scheduling screening colonoscopy.  
159 Please call XXX-XXX-XXXX to schedule your colonoscopy right away.  
160

161 Call the VIP hotline XXX-XXX-XXXX to schedule your screening colonoscopy!  
162

163 **Active Choice**

164 Our records show that you may be overdue for your colon cancer screening  
165 Penn Medicine is offering a special VIP hotline to patients for scheduling screening colonoscopy.  
166 Please call XXX-XXX-XXXX to schedule your colonoscopy right away.  
167 Alternatively, you may choose to instead complete and return the enclosed stool test called FIT (Fecal  
168 Immunochemical Test).  
169

170 Call the VIP hotline XXX-XXX-XXXX to schedule your screening colonoscopy  
171 -or-  
172 complete and return your FIT today!  
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**Reminder Outreach**

**Colonoscopy Only**

Our records show that you may be overdue for your colon cancer screening  
Penn Medicine is offering a special VIP hotline to patients for scheduling screening colonoscopy.  
Please call XXX-XXX-XXXX to schedule your colonoscopy right away.

Call the VIP hotline XXX-XXX-XXXX to schedule your screening colonoscopy today!

**Sequential Choice**

Our records show that you may be overdue for your colon cancer screening  
Penn Medicine is offering a special VIP hotline to patients for scheduling screening colonoscopy.  
Please call XXX-XXX-XXXX to schedule your colonoscopy right away.  
Alternatively, you may choose to instead complete and return the enclosed stool test called FIT (Fecal  
Immunochemical Test).

Call the VIP hotline XXX-XXX-XXXX to schedule your screening colonoscopy  
-or-  
complete and return your FIT today!

**Active Choice**

Our records show that you may be overdue for your colon cancer screening  
Penn Medicine is offering a special VIP hotline to patients for scheduling screening colonoscopy.  
Please call XXX-XXX-XXXX to schedule your colonoscopy right away.  
Alternatively, you may choose to instead complete and return the enclosed stool test called FIT (Fecal  
Immunochemical Test).

Call the VIP hotline XXX-XXX-XXXX to schedule your screening colonoscopy  
-or-  
complete and return your FIT today!