PILOTING INTERVENTIONS TO IMPROVE ADHERENCE TO CERVICAL CANCER SCREENING RECOMMENDATIONS AMONG EMERGENCY DEPARTMENT PATIENTS

Principal Investigator – David Adler, MD, MPH

I. PURPOSE OF THE STUDY AND BACKGROUND

Cervical cancer is among the most preventable forms of cancer. Implementation of widespread cervical cancer screening has resulted in a tremendous decrease in the incidence of cervical cancer in the United States and stands as a cornerstone of preventive health efforts. Still, only 80.7% of U.S. women aged 21 – 65 years report adherence to U.S. Preventive Services Task Force (USPSTF) cervical cancer screening recommendations[1]. This rate is far below the *Healthy People 2020* target of 93%[2]. The group identified as most likely to be non-adherent with recommended screening protocols are patients who use the emergency department (ED) for their usual source of care[1,3]. **The overall goal of the proposed study is to pilot two brief behavioral interventions aimed at improving adherence to cervical cancer screening among ED patients.** The results of this pilot will prepare our interdisciplinary team to successfully compete for NIH funding to scale up the evaluation of the proposed interventions. In order to achieve this goal, we propose to leverage an existing parallel service program in the high volume general population setting of the URMC ED to accomplish the following specific aims:

Specific Aim 1: Conduct a randomized pilot trial comparing the efficacies of two structured behavioral interventions in promoting adherence of women aged 21 – 65 to USPSTF cervical cancer screening recommendations: A. Screening & referral and, B. Screening, brief mobile technology-based intervention grounded in the Theory of Planned Behavior (TPB)[4], & referral.

Hypothesis 1A/1B: The proposed interventions will improve adherence to USPSTF recommendations at follow-up over baseline levels. Rates of adherence will be greater after Intervention B compared to A.

Specific Aim 2: Identify predictors of adherence and non-adherence to USPSTF recommendations at baseline to inform the refinement of the proposed interventions.

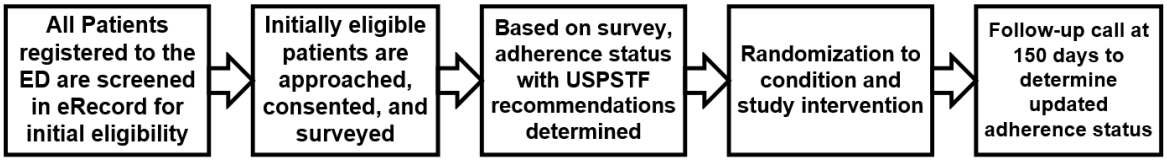
Hypothesis 2: Lower baseline rates of adherence will be identified among ethno-racial minorities, as well as among women with less education, without a usual source of care, and with greater barriers to care.

Specific Aim 3: Collect qualitative feedback on perceptions of the interventions to inform their refinement.

II. STUDY DESIGN

a. Screening, Enrollment, & Randomization. The proposed pilot study will utilize a randomized, prospectively collected, convenience sample and a short-term longitudinal design. Our approach is summarized in Figure 1 and detailed below. EDRAs will use the EPIC eRecord system to screen adult patients that are registered in the ED at URMC for eligibility over a four-month period. Inclusion criteria will include: female, age 21 – 65 years. Exclusion criteria will include past hysterectomy with cervical removal, known infection with HIV (as screening recommendations for women with HIV differ from the general population), inability to consent (e.g., lacking decisional capacity, intoxicated, or in distress), non-English speaking, or lack of text-capable mobile phone and/or inability to use text function. Eligible women will then be approached by a representative of the EDRA program who will read a brief script describing the study and inviting the patient to enroll. Consent documentation will be completed for all enrollees. Based on previous studies with a similar level of patient involvement utilizing our EDRA program, we anticipate an enrollment rate of >85% of eligible participants, such that approximately 530 women will be approached.

Figure 1. Project Workflow



450 patients enrolled over 4 month period

After consent, enrollees will complete a ~10-minute computer-adaptive questionnaire, administered at the bedside on a tablet computer by the EDRA to determine adherence to current USPSTF recommendations for cervical cancer screening[15]. The REDCap adaptive screening tool used will be identical to that which was used to gather our preliminary data[14]. The enrollment process will categorize study participants into three groups: adherent, uncertain, or non-adherent (Figure 2). Women found to be adherent will be notified and their participation will conclude (i.e. no follow-up will be performed). Women found to be in the uncertain or non-adherent groups will then be randomized into one of two intervention conditions. Randomization will be automated in the REDCap survey instrument. All women found non-adherent will be referred to their usual care provider. If the patient does not have a usual provider of women's healthcare, she will be referred to UR WHP to receive appropriate screening. Dr. Bonham (co-I) will maintain an expedited referral pathway to UR WHP for these subjects. Dr. Bonham or one of the other health care providers at WHP will conduct the screening test. Women for whom adherence is uncertain (e.g. unsure, unable to remember) will be referred to their usual care provider or to UR WHP to confirm their adherence status. If, upon follow-up, the patient was confirmed adherent, she will be retroactively classified as adherent at baseline (though her uncertain status at screening will be retained in the dataset for potential secondary analyses). If confirmed non-adherent, the patient will be retroactively classified as non-adherent at baseline (with initial uncertainty retained). If the patient did not contact a provider to confirm adherence status (and did not remember her status in the 150 day interim), she will remain classified as uncertain.

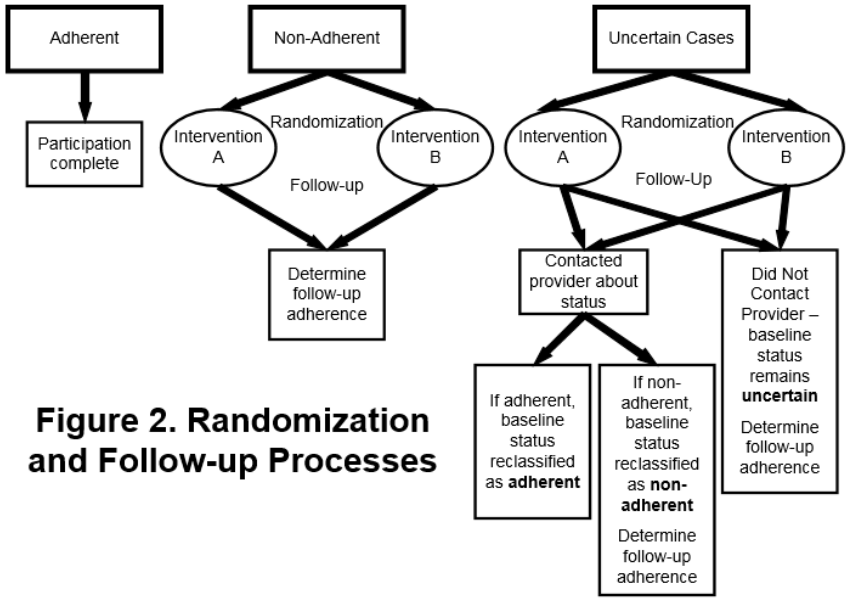


Figure 2. Randomization and Follow-up Processes

b. Description of Interventions. The proposed study pilots two interventions aimed at improving adherence to guidelines by encouraging screening outside of the ED. **Intervention A** only involves screening for adherence status and referral of uncertain and non-adherent patients for screening and/or confirmation of status and screening. **Intervention B** follows the Screening, Brief Intervention, and Referral to Treatment (SBIRT) model popularized in the substance use literature in the ED [16-18]. The three components of the TPB intervention will be delivered via a series of text messages to mobile phones. Patients will receive a total of three text messages at 30-day intervals between the ED index visit and telephone follow-up survey at 150 days. Each text message will include a statement directed towards one of the TPB predictors of behavioral change intentions (Table 1) accompanied by a reminder to schedule cervical cancer screening with their primary provider or the WHP. Attitudes regarding cervical cancer screening will be addressed by emphasizing its efficacy for preventing morbidity. Subjective normative beliefs about screening will be addressed by emphasizing the preponderance of adherence to guidelines in the population. Perceived behavioral control over obtaining cervical screening will be addressed by discussing the accessibility and negligible financial burden of Pap tests. Women who have their own women's health providers will be instructed to follow-up with these providers or utilize UR WHP, whichever they prefer. To facilitate patient follow through, the message will include hyperlinks to the telephone numbers of the patient's women's health care provider (if known) and the WHP.

Table 1 – Theory of Planned Behavior Texts to Participants in Intervention B

Element of the TPB	TPB portion of text	Scheduling portion of text
Attitudes about Screening	"Regular screening for cervical cancer is an extremely effective way to prevent cancer or identify early stages of cancer that can be effectively treated"	Schedule cervical screening by calling your usual women's health provider at {Participant-specific phone number} or with UR Women's Health Practice at 585-275-2691
Subjective Norms about Screening	"Over 80% of women across the country stay up-to-date with cervical cancer screening guidelines."	
Perceived Behavioral Control over Obtaining Screening	"Pap tests are available, without cost to you, at your women's health provider or at the UR Women's Health Practice."	

c. Follow Up. All enrollees in the non-adherent and uncertain groups will receive a follow-up call at 150 days (Figure 3). The project coordinator will contact each of these participants by telephone for a brief REDCap questionnaire to determine if they underwent screening, if they learned that they did not require screening, and what barriers they perceived in getting screened or clarifying their adherence. Qualitative feedback regarding perceptions of the interventions will also be solicited from study participants in order to refine the interventions for future study. Relevant domains of feedback will include challenges to adhering with screening guidelines, comfort level with the intervention content discussed in the ED, which TPB message(s), if any, were perceived as most generative of intention to engage in cervical cancer screening, and participant recommendations for intervention revision. Telephone numbers will be confirmed in the ED during enrollment by the EDRA performing the enrollment (e.g., calling patient's phone to be certain the number is correct), and up to 3 calls will be made to each of these patients to limit unnecessary attrition.

Study team members will use the EPIC medical record to confirm self-reported screening activities among the subjects successfully contacted at follow-up and who report a women's health provided associated with UR Medicine. No confirmation will be sought among subjects reporting cervical screening with providers outside of the UR Medicine system.

A limited medical record review will be conducted for all enrolled subjects to determine cervical cancer screening activities and results through providers associated with UR Medicine in the prior 5 years. These data will be compared to self-reported screening activities to demonstrate the validity of the study procedure used in the current study. These data will also be used to determine the extent to which subjects are aware of their suggested screening schedules based on history (e.g., abnormal Pap test results, positive high-risk HPV test).

III. CHARACTERISTICS OF THE RESEARCH POPULATION
a. Number of Subjects: 450

b. Gender and Age of Subjects: Women age 21-65. Cervical cancer only occurs in women and cervical cancer screening is only recommended for women aged 21 – 65.

c. Racial and Ethnic Origin: We expect the racial and ethnic characteristics of our study population to mirror that of the general patient population of the Emergency Department at Strong Memorial Hospital.

d. Vulnerable Subjects: N/A

e. Inclusion Criteria:
- Women
- Age 21 - 65

f. Exclusion Criteria:
- Past hysterectomy with cervical removal
- Known infection with HIV (screening recommendations for women with HIV differ from the general population)
- Non-English speaking
- Inability to consent
- Lack of text-capable mobile phone and/or inability to use text function

IV. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT
a. Method Of Subject Identification And Recruitment
Emergency Department Research Associates (EDRAs) will use the EPIC eRecord system to screen adult patients that are registered in the ED at URMC for eligibility over a four-month period. Eligible women will then be approached by a representative of the EDRA program who will read a brief script describing the study and inviting the patient to enroll. Consent documentation will be completed for all enrollees. Based on previous studies with a similar level of patient involvement utilizing our EDRA program, we anticipate an enrollment rate of >85% of eligible participants, such that approximately 530 women will be approached.

b. Process of Consent
EDRAs will conduct the consent process using RSRB-approved consent documents. Subject will be encouraged to ask questions and to confirm comprehension. Consent documents will be stored in locked cabinets in the Emergency Medicine Research office suite in the Saunders Research Building.

V. METHODS AND STUDY PROCEDURES
a. Data Banking for Future Research Use
Data obtained from the study will be stored for future analyses. This plan will be made expressly

clear in the consent document. All identifiers will be deleted from the data set after follow-up is completed.

b. Costs to the Subject

There will be no cost to study subjects.

c. Payment for Participation

There will be no payment to subjects for participation.

d. Return of Individual Research Results

Research results will not be provided back to the subjects.

VI. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Subjects withdrawn from the study will not be replaced.

VII. SAFETY AND REPORTABLE EVENTS

a. Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

b. Serious Adverse Event

No serious adverse events related to this study can be reasonably expected to occur. A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

c. Recording Adverse Events

At each subject visit (i.e. index/enrollment visit in emergency department and follow-up phone call) the site study staff will assess adverse events by recording all voluntary complaints of the subject. At each study visit, the subject will be questioned directly regarding the occurrence of any adverse experience related to the study. All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, will be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, and the relationship to the study.

d. Responsibilities for Reporting Serious Adverse Events

No serious adverse events related to this study can be reasonably expected to occur. In the event of an SAE the RSRB will be notified immediately.

VIII. RISK/BENEFIT ASSESSMENT

a. Potential Risks

The primary risk of this study is breach of confidentiality regarding the information you provide to us. The other potential risk is the bother of receiving text messages (study subjects will receive a maximum of 3 text messages) and of receiving the follow-up phone call.

b. Protection Against Risks

Only members of the study team will have access to the study information and all data will be kept in password-protected computers and/or in locked cabinets. No more than three attempts will be made to conduct the follow-up telephone call.

c. Potential Benefits to Subjects
The potential benefit a subject might have from participation is getting up-to-date on cervical cancer screening which is essential to identify treatable pre-cancerous lesions of the cervix before they progress to cancer.

d. Alternatives to Participation
There are no alternatives to choosing not to participate in this study. Standard of care in the ED will not be impacted by the decision to participate.

IX. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE
All electronic study data will be kept on password protected University drives. All paper data (e.g. consent documents) will be kept in locked storage cabinets in the Emergency Medicine Research suite in the Saunders Research Building.

X. RESEARCH INFORMATION IN MEDICAL RECORDS
Research Data will not be included in the subject's medical record.

XI. DATA ANALYSIS
a. Plan of Analysis. Based on previous research[1,19,20] and our preliminary data, we anticipate ≥18% of patients will be non-adherent to screening guidelines. As such, we will enroll 450 patients to identify ≥90 non-adherent patients. To test **Specific Aim 1 - Hypotheses 1A/1B**, we will use (a) a one sample test of improvement in adherence at follow-up and (b) a two-sample comparison of post-intervention adherence across intervention conditions. These analyses will allow us to establish preliminary effect sizes for powering the subsequent NIH submission. The first test will compare % adherent at follow-up against a null value of 15% improvement (i.e., % of non-adherent subjects who would become adherent over 150 days without intervention). We think this is an unrealistically high null value, but it was chosen to avoid overestimating the impact of the study interventions. Using this null value, a one-tailed test with $\alpha=0.05$, and ≥ 90 non-adherent subjects across conditions, we will have power of 0.80 to observe improvement as small as 10% over the null (40% relative improvement). The second test will use χ^2 to compare conditions. Given a one-tailed test with $\alpha=0.10$ and 45 non-adherent subjects in each condition, we will have power of 0.70 to observe a difference as small as 24% in adherence at follow-up. More importantly, we will establish a 95% confidence interval around the overall improvement rate (across conditions) with ≤10.4% margin of error and intervention specific rates of improvement with ≤14.8% margin of error. These intervals will allow us to calculate power for the subsequent trial under expected, ideal, and worst-case scenarios. Patients lost to follow-up will be considered intervention failures (i.e. non-adherent) in accordance with intention-to-treat principles. In order to test **Specific Aim 2 - Hypothesis 2**, we will use hierarchical, multinomial logistic regression to predict adherence at baseline. Given our sample size and an expected adherence rate of 0.80, at $\alpha=0.05$, we will have power ≥0.70 to observe odds ratios as small as 1.33. Any covariates demonstrating a p-value ≤ 0.10 will be addressed when refining the interventions for the subsequent NIH trial. **Specific Aim 3** is focused on the qualitative feedback data collected at the 150-day follow-up call. Qualitative data analysis of the feedback data will include open and axial coding under Grounded Theory principles[21] examined in the context of subject demographic characteristics. The codes/concepts that emerge from these data will be examined in the context of the demographic characteristics of the subjects providing feedback. Results will then be used to refine the intervention protocols for the subsequent efficacy trial.

b. Additional Analyses. Supplemental analyses will be performed in order to strengthen interpretations of potential intervention effects. Specifically, we will perform the analyses described above among only those women who were referred to UR WHP (i.e., those without a usual provider of women's healthcare). Although we are not specifically powering our study around this subset of subjects, these analyses may help us identify success within this underserved population or important covariates/barriers than must be addressed when intervening with subjects lacking a usual women's healthcare provider. We will also corroborate subject self-reports of contact and screening using UR WHP records and subject eRecords (for those with providers associated with UR Medicine) as a way to further validate the findings observed. Finally, we will evaluate over-referral in our study by examining the percentage of women deemed to have uncertain adherence status who are reclassified as adherent, as well as those potential individuals deemed non-adherent in our study who find they are adherent through their women's healthcare providers. This rate of over-referral will be useful when evaluating the impact of the interventions on both subject health and clinical resource utilization.

XII. DATA AND SAFETY MONITORING PLAN

Oversight of the trial is provided by the Principal Investigator (PI), Dr. David Adler. Dr. Adler assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Study data are accessible at all times for the PI and co-investigators to review. The PI and co-investigators will review study conduct (e.g. accrual, protocol deviations) on a weekly basis. The PI and co-investigators will review(s) AEs individually in real-time and in aggregate on a monthly basis. Although no SAE's can be reasonably expected to occur from a study of this nature, the PI will review any serious adverse events (SAEs) in real-time. The PI ensures all protocol deviations, AEs, and SAEs will be reported to the RSRB according to the applicable regulatory requirements.

Adverse events and serious adverse events are defined as above. Adverse events are graded to the following scale:

Mild: An experience that is transient, & requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

AEs are identified at the two points of contact with study subjects (i.e. index/enrollment visit to the emergency department and the follow-up telephone call) or if contacted by a study subject at any time. No AEs are expected. No SAEs are expected.

XIII. REFERENCES

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