

# **Study Protocol**

**Version 1.0**

Randomized Trial to Increase Adherence to Cervical Cancer  
Screening Guidelines for Young Women

*Decreasing Overtreatment and Screening (DOTS) Study*

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## **PROJECT SUMMARY**

**BACKGROUND** Screening with cytology has accompanied large decreases in cervical cancer mortality in the US. However, cytology remains a relatively non-specific test resulting in needless invasive procedures for many women. Studies show that young women are specifically vulnerable since over-screening results in overtreatment with excisional therapies that have been associated with premature delivery and emotional distress. Current national guidelines recommend that routine screening be performed at less-frequent intervals and excisional cervical therapies are discouraged in young women. Uptake of these guidelines has been low for several reasons: many women expect annual cytology, physicians may have financial incentives and/or are not aware of current guidelines. **OBJECTIVES** To examine physician- and patient-based interventions designed to decrease overscreening and overtreatment by increasing adherence to US guidelines for women under 30 years of age. Specifically, the interventions will focus on increasing average intervals between screening and decreasing the number of excisional procedures. The long-term objective is to identify effective strategies to increase adherence to screening guidelines nationwide. **METHODS** We will conduct a randomized intervention clinic with two arms and use Family PACT administrative data for sampling, baseline, and outcome assessment. We will select 14 clinics from the Family PACT provider network that evaluate at least 200 female clients under 30 years of age per year. Clinics will be randomized to 1 of 2 arms: 1) mobile application (APP)-based intervention for providers, and 2) APP-based intervention for providers plus patient-centered approach (PCA) intervention. These groups will be compared to a comparison group of 7 clinics chosen at random (those not randomized). The APP intervention is for clinicians' mobile phones and will maneuver them through current guidelines based on age and condition. The PCA intervention will be patients' education using a tablet at the time of check-in to assist in understanding guidelines, asking questions of their providers, and assist them in evaluating treatment options. Family PACT serves predominantly uninsured women and 40% of clients are Latina. Development of the interventions will be conducted with input from all stakeholders including women from the community who are members of the National Cervical Cancer Coalition, and the Latina Contra Cancer, the American Congress of Obstetricians and Gynecologists, the State Office of Family Planning, the American Society for Colposcopy and Cervical Pathology and Quest laboratories. We plan to enroll 7 sites into each intervention arm with an average of 2800 to 3500 women aged 21-29 years per arm with a similar number of sites and women randomly chosen for the comparison arm resulting in a total of 21 sites and 8400-10500 women. Outcomes will be compared between study arms using t-test adjusting for clustering by clinic. **PATIENT OUTCOMES** We will use Family PACT claims data to calculate for each clinic by age, the number of and average interval between cytology specimens, colposcopy examinations and the number of excisional procedures. **SIGNIFICANCE** We will define successful interventions that will reduce unnecessary screening and treatment for cervical cancer screening in young women.

## **STUDY TEAM**

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## **STUDY GOAL AND OBJECTIVES**

### **Study Goal:**

This study's goals are to increase physician and patient adherence to cervical cancer screening guidelines with the ultimate aim of obtaining better health and well-being for women under 30 years of age.

### **Study Objectives:**

To examine physician- and patient-based interventions designed to decrease overscreening and overtreatment by increasing adherence to US guidelines for women under 30 years of age. Specifically, the interventions will focus on increasing average intervals between screening and decreasing the number of colposcopy examinations and excisional procedures. The long-term objective is to identify effective strategies to increase adherence to screening guidelines nationwide.

## **BACKGROUND AND SIGNIFICANCE**

### **Impact of Condition on Health of Individuals and Populations**

Beginning in the 1950's routine screening for cervical cancer began in the U.S. using Papanicolaou smear or cytology. Since then, rates of cervical cancer in the U.S. have decreased by more than 60% specifically in women aged 30 years and older.<sup>1</sup> The age distribution of cervical cancer shows that young women (those 30 and younger) rarely develop cervical cancer with rates less than 2 per 100,000. After 30 years of age there is a rise in CC incidence with a median age of 47 years. This observation is closely linked to the natural history of HPV, the cause of cervical cancer. High risk (HR) HPV infections are those types associated with cervical cancer.

HR-HPV is an extremely common sexually transmitted infection that begins shortly after the onset of sexual activity.<sup>2,3</sup> Partner studies show that HPV is easily transmitted between couples with estimated transmission of 100% after 11 acts of sexual intercourse.<sup>4,5</sup> Lifetime risk of acquiring a cervical HPV infection is around 80%. HPV is most commonly found in women 25 year and younger with prevalence rates around 20%. Notably, there is a decline in prevalence starting around 30 years of age which is time where CC begins to rise.<sup>6</sup> The high rates observed in young women is closely paralleled by the high rate of low grade abnormalities on cytology in this age group.<sup>7</sup> We now know that these low grade abnormalities are merely benign reflections of active viral replication. We also now know that most (90%) of women will show clearance of these infections which is thought to occur through both innate and adaptive immune responses which likely protect women from re-infections explaining the decline of HPV with age.<sup>6,8,9</sup> On the other hand, persistent HPV infection is the cause of cervical cancer and data shows that cervical cancer develops only after years to decades of HPV persistence in the majority of women which explains why young women rarely have cervical cancer and why in a women's 40's her risk increases. Although cytology is used to detect early invasive cancers, it is now used predominantly to detect precancers, which can be easily treated with several modes of therapy. Of note, there has been virtually no change in cancer rates over the last 10 years.<sup>1,10</sup> This is predominantly due to the limits of cytology. Unfortunately, screening cytology remains relatively insensitive missing approximate 40-50% of significant precancers found on biopsy. Most now refer to the diagnosis of cervical intraepithelial neoplasia (CIN) grade 3 as the only "true" significant precancer and the lower grade CIN 1 as completely benign. CIN 2 diagnosis remains more controversial and discussed later. However, the cytologic categories have used the Bethesda terminology, which uses only two grades: low (L) grade and high (H) grade squamous intra-epithelial lesions (SIL). Recently there has been consensus to use these same terms for histology where CIN 2 and 3 are considered HSIL and CIN 1 is LSIL.<sup>11</sup>

The insensitivity of the cytology to detect CIN 3 led to frequent screening (annually) and the referral of diagnosis that described insignificant disease. The latter occurred because LSIL and HSIL often co-exist. It is not unusual that only cells from LSILs are detected on the cytology smear in women who also have HSIL for reasons not clear but may be that the LSIL cells are shed more easily. Hence current practice guidelines recommend referral of adult women with LSIL as well as HSIL to colposcopy triage where directed biopsies are taken of tissue that appears abnormal.<sup>12,13</sup> To complicate matters, a more subtle cytologic diagnosis was created referred to as Atypical Squamous Cells of undetermined significance (ASCUS) which were considered not normal but not SIL. The problem remains that the majority of women with



ASCUS or LSIL on cytology have either no disease or LSIL on biopsy and the majority of women with the true HSIL have ASCUS or LSIL on cytology and not HSIL. In a recent meta-analysis<sup>14</sup>, the sensitivity and specificity of detecting CIN 2 or worse was 57 and 97%, respectively if HSIL was used as a cut off—using LSIL, it was 76% and 81%, respectively. The natural history of LSIL shows that over 90% of women with this lesion will have spontaneous regression, hence, treatment of these lesions would be uncalled for in most.<sup>15,16</sup> HSIL, on the other hand, is considered a true precancer with progression rates to cancer ranging from 5 to 30%.<sup>17</sup> On the other hand, regression rates of HSIL have been reported as high as 70%, specifically in young women.<sup>18,19</sup> The progression potential of HSIL remains somewhat elusive since HSIL is a mixture of CIN 2 and 3 lesions.<sup>20</sup> Many believe that CIN 2 does not exist and is simply a misdiagnosis of either a lesion that is truly a CIN 1 or a CIN 3.<sup>21</sup> Numerous studies have shown that cytologic and histologic diagnosis are relatively subjective and have poor reproducibility rates between pathologists for all grades of CIN.<sup>22</sup> Very recently, p16 staining, a marker of cell dysregulation induced by HPV, is being used to adjudicate CIN 2 lesions.<sup>20,23,24</sup> It is now recommended that lesions diagnosed as CIN 2 by a pathologist be stained for p16 and if negative for p16 staining, the lesion should be downgraded to a CIN 1, or now referred to as LSIL and if positive, categorized as HSIL.<sup>11</sup>

Using ASCUS or LSIL as a cut off results in referring thousands of women who do not need colposcopy and biopsy whereas using HSIL as a cut off results in missing significant disease including cancer. Biopsy is also not without risk in that infection or bleeding, although rare, can occur. Treatments for abnormal biopsy results include ablative (i.e. cryotherapy (freezing), electric dissection, cold coagulation and laser ablation) and excisional (i.e. Loop electrosurgical excision therapy (LEEP), laser conization and cold-knife conization). None of these procedures are without risk. All can be associated with pain, bleeding and infection as well as psychological distress, anxiety and fear.<sup>25,26</sup> LEEP has become the modality of choice for most practitioners. Cryotherapy has lost appeal since treatment with cryotherapy of large lesions can result in recurrences and excisional therapies allow the margins of the lesions to be evaluated by a pathologist.<sup>27</sup> Although controversial, margins with evidence of disease are more commonly associated with recurrences. There have been a few meta-analysis and systematic reviews examining birth outcomes after CIN treatment. Crane et al<sup>28</sup> in systematic review found that women who had LEEP were more likely to have preterm birth (OR =1.81 95% Confidence Interval (CI) 1.18, 2.76) and low birth weight infants (<2500 g) (OR=1.60, 95% CI 1.01, 2.52; P = .04). No differences were found in C-section, labor induction or neonatal intensive care unit admission. The finding for preterm birth persisted even when controlling for smoking status. In a prospective study, Crane and colleagues<sup>29</sup> reported that LEEP and cold knife procedures were both associated with preterm birth. Two small meta-analysis found that excisional but not ablative treatment was associated with preterm birth<sup>30 31</sup>. A recent meta-analysis of excisional and ablative therapies by Bruinsma and Quinn<sup>32</sup> found that preterm birth was increased in women who received excisional therapy compared to both a population based (OR=1.97 95% CI 1.78-2.17) and hospital based (OR=2.71 95% CI 1.89-2.49) comparator. Ablative treatment was also associated with increased risk compared to population-based comparators (OR=1.53 95% CI 1.32-1.78) but not Hospital- based. This meta-analysis also compared treatment to women with CIN but no treatment. In this comparison, excisional (OR=1.25 95% CI .98-1.58) had a smaller affect and ablative was not significant (OR = 1.03 95% CI 0.9-1.18).

## **Screening and Management Guidelines**

Between the 1940s and 2002, women in the U.S. were advised to have cytology screening for cervical cancer performed annually at the time of their well woman visit. Although initially this results in a rapid decline in cervical cancers, little to no change has occurred in most population over the past decade. As reviewed above, studies now show that overscreening may result in overtreatment with excisional therapy which has negative consequences such as premature delivery. Over the past decade, national guidelines have changed substantially to avoid negative outcomes, such that routine screening is started later in life, completed earlier, and performed at greater intervals. In addition, it is advised to observe and follow cytologic and histologic abnormalities in young women rather than perform invasive procedures.

Recently there were several updates to both cervical cancer screening guidelines and management of abnormal cytology and histology. The American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology and American Society for Clinical Pathology sponsored a systematic evidence review of the ACS guidelines regarding screening for early detection of cervical precancerous lesions and cancer.<sup>33</sup> In parallel, the US Preventive Task Force also reviewed and updated their guidelines.<sup>34</sup> Based on evidence that HPV is extremely common in young women and cancer is extremely rare under the age of 21, it is now recommended that cervical cancer screening not begin until the age of 21 years. It was emphasized that overscreening and overtreatment in this group represents a net harm over underscreening. For women aged 21-29 years, it is recommended that women are screened with cytology along every 3 years and that HPV testing not be used to screen women in this age group, either as a stand-alone or HPV co-test. These guidelines were derived mostly from modeling studies. It was noted that annual screening resulted in twice the number of colposcopies compared with screening every 3 years.<sup>35</sup>

In addition, the 2006 consensus guidelines for management of abnormal cytology and histology<sup>12,13</sup> were updated.<sup>36</sup> For women under 26 years of age with abnormal cytology and histology, observation with cytology and colposcopy is recommended over invasive treatments such as LEEP and cryotherapy. More specifically, for young women with ASCUS and LSIL, it is recommended to repeat cytology annually and refer to colposcopy only if persistent at 2 years or if HSIL develops. Recommendations continue from the 2006 guidelines that young women with HSIL (CIN 2,3), defined as those interested in fertility, be followed by colposcopy and cytology rather than immediately referred for therapy<sup>36</sup>.

Adherence to these screening and management guidelines has been disappointingly low<sup>37</sup>, although the adherence to other national guidelines in general is low.<sup>38-40</sup> Dissemination and implementation of these guidelines can be a challenge in the US--many women equate health care with annual Pap smears and continue to demand these examinations. In addition, many physicians may have financial incentives to over screen and treat or are not aware of current guidelines.

This research will be expected to influence adherence to guidelines and lead to improved patient health and well-being as this study would show interventions that are capable of lowering the number of unnecessary colposcopic examinations, cervical biopsies and excisional therapies. All of these procedures have been shown to have negative effects including psychological distress

and premature delivery. Numerous providers and stakeholders have underscored the need to avoid these unnecessary procedures.<sup>33,36,41,42</sup>

There has been little done regarding physician based interventions regarding cervical cancer screening. In general, message based interventions (i.e., messages on laboratory reports), payment denials, and electronic medical record messages have all been examined with mixed results.<sup>43</sup> Newer technologies have not been evaluated extensively in any setting. These include offering free applications (APPs) for mobile phones, which would give easy access to guidelines. In addition, no mobile application intervention for patient decision-making has been applied for cervical cancer screening.

The aims of this study will specifically examine different strategies to increase physician and patient adherence to guidelines with the ultimate aim of obtaining better health and well-being for the woman. To date, no data is available on patient-centered interventions to assist the patient in understanding the guidelines and making informed decision on treatment options. It is important to have a team of experienced researchers, educators, and community stakeholders along with patient input to develop patient centered models. In addition, although mobile applications are becoming more common, there are no studies that have evaluated their success in increasing provider adherence to guidelines.

We also have the unique opportunity to work with the California Office of Family Planning: Family PACT program which serves underinsured women to obtain several preventive care services including cervical cancer screening. This innovative study will take advantage of the Family PACT claims database, which would give us the opportunity to examine reimbursement requests before and after intervention to assess the efficacy of the interventions. This type of outcome data avoids several biases associated with measuring efficacy of interventions.

The results from this research would influence current practice, which would lead to the decrease in unnecessary cervical procedures, and in turn would result in less premature birth and decreased distress caused by these procedures. Our relationship with all of our stakeholders would result in rapid dissemination of the results within Latina communities with the assistance of Latina Contra Cancer, national communities of patients with the assistance of National Cervical Cancer Coalition and our organizational stakeholders, American Society for Colposcopy and Cervical Pathology and American Congress of Obstetrics and Gynecology which both have large member associations and numerous opportunities through their organizations for dissemination.

### **Impact on Health Care Performance**

The development of guidelines are centered toward reviewing the most recent literature so that evidence-based decisions can guide development of guidelines that are based on our best understanding of benefit and harm with each strategy and outcome. Several standards have now been assigned to the review of the literature including a systematic review and weighing of the evidence.<sup>44</sup> The most recent evidence suggested that overscreening women results in more harm than benefit and over treatment is not only costly but has negative effects including psychological distress and premature birth (reviewed above). Modeling studies all showed that these new guidelines are likely to be quite cost-efficient.<sup>35,45-48</sup> Data analysis that was performed for the USPTF decision for screening young women every 3 years showed that there were less

colposcopies and less cervical cancer cases for screening every 3 years with cytology and HPV testing starting at 30 than screening every 3 years with cytology alone for all ages.<sup>35</sup> The age at which HPV testing begins to play an important role is 30 years of age when most HPV infections when detected reflect already persistent infections. Until then, most infections are thought to be more recently acquired or have not had adequate change to spontaneously regress. Therefore, cytology alone is best used under 30 years of age. These data support that non-adherence to the guidelines is likely to result in inefficient patient care. As discussed above<sup>33</sup>, there is good evidence that many providers do not adhere to the new guidelines including age of first cytology, screening intervals and overtreatment specifically in young women.<sup>41,49-52</sup> Therefore, interventions to decrease overscreening and overtreatment according to the current guidelines will increase the efficiency of patient care and we believe it will also improve the overall quality and experience of their care. We also believe that the patient centered approach will be most efficient since it offers an opportunity for teaching which would then in turn decrease time required of the physician. Patient-centered approach is to educate the patient so that she is armed with critical information to understand the guidelines, ask more focused questions of the provider and ultimately to assist the patient in making informed decisions. The guidelines themselves are very complicated and it is not expected that the patient should be able to maneuver through the guidelines, however, simple messages can be understood by patients who then can assist them to feel comfortable with the new guidelines, and in the case of treatment options, make a decision that they are also more comfortable with making. However, it is likely that a successful intervention will be required for both patients and providers as discussed above.

We believe this project would increase the efficiency of patient care with less unnecessary cytology specimens, less unnecessary referral to colposcopy and biopsy and most important less invasive treatment for CIN in young women that in turn would result in less premature births.

### **Relevance to Patients**

Although referral to colposcopy may seem benign, studies have shown that many women are negatively affected by a diagnosis of an abnormal Pap test or HPV tests including feelings of shame, anxiety, fear, and emotional distress.<sup>25,53-55</sup> Relationships are often negatively affected as well when trying to explain the sexually transmitted nature of HPV. Referral to colposcopy also affects work and school activities. Colposcopy and biopsy itself is associated with psychological distress, anxiety and fear.<sup>53,56-58</sup> Most women find biopsy uncomfortable and excisional therapies often quite painful. On the other hand, the fear of developing cervical cancer is overwhelming to many women and these women are comforted by having annual examinations that include cervical cancer screening. Cervical cancer screening is always a balance between harm and benefit and this balance is age related. Some younger women may think that since they have received the HPV vaccine that no screening is required. However, since the vaccine only covers 2 of the 15 high-risk types, screening in this population also remains essential and this message must be conveyed.

This proposed research is focused on developing tools that will decrease anxiety and fears about HPV, undo myths and enhance women's participation in obtaining regular health care including appropriate cervical cancer intervals.

## **STUDY DESIGN**

### **Overview**

This is a clustered randomized trial with individual clinics serving as the clusters. Clinics from the California Family PACT provider network who serve at least 200 female clients per year <30 years of age will be randomized to one of 2 intervention arms: 1) physician based approach (APP), and 2) APP-based intervention plus patient-centered approach (PCA). We will reach out to eligible sites to identify which sites are willing to participate. Of these, we will randomize 14 clinics to one of the two intervention arms. These groups will be compared to a comparison group (those not randomized). Since Family PACT data is available for all sites, randomization is not necessary for the comparative groups. However, attention to size, cultural make-up and public versus private information will be accounted for in identifying 7 sites for comparison. Seven sites in each arm/group will result in an average of 2800-3500 women per arm/group—total of 8400-10500 women.

### **Study Population**

In FY 2012-13, 2,297 Family PACT clinician providers served over 1.5 million female Family PACT clients. A detailed description of the Family PACT services can be found in the Family PACT Program report for FY 2012-13. Women eligible for these services are uninsured women, under 200% of the federal poverty level, at risk of pregnancy. Sixty-three percent of Family PACT female clients are less than 30 years of age and about 50% are within our target age group: 21-29 years. Sixty-three percent define themselves as Latina and 38% report that Spanish is their primary language. Twenty percent identified as white and 6% as black. Eighty percent were below the Federal Poverty Guidelines. Retention at clinics is quite high. Defining retention as having used Family PACT at least once in four years prior to their visit in FY 2012-13, 74% were retained in care. The program serves a disproportionately high number of Latinas. Fifty-three percent of the entire Family PACT population is Latina, whereas 19% of the entire California population is Latina.

Our goal is to identify 14 provider sites that each serve at least 200 female clients aged 21-29 years that are willing to participate in study and be randomly assigned to one of the two research arms. We will also identify sites with similar inclusion criteria who but are not participating and of these, 7 sites will be randomly selected for comparison so that this comparison arm would result in a similar number of women aged 21-29 years. We will use variables from the following Family PACT administrative databases to determine the sampling universe: Provider enrollment, client enrollment, and claims databases. We excluded Family PACT providers who are Planned Parenthood (PP) affiliates from our sampling universe because they have a unique monitoring and tracking system of cervical cytology testing that assures adherence to guidelines hence, they would not be representative of other primary care settings. We will also exclude those that already have on average long intervals (>30 months) since they likely already adhere to guidelines. To maintain efficiency, we will focus on Southern California sites that serve the greatest number of women. These include Los Angeles, Orange, San Diego, Riverside, Santa Barbara, San Bernardino, Imperial, Kern, Ventura, and Fresno counties. Within these counties, there are 1,114 private sector clinics, 456 public sector clinics serving a total of 1,280,846 clients. The average age of these women is 27.4. Sixty-nine percent identify as Latina, 15% as white, 6% as black, and 7% as Asian/Pacific Islander. Forty-six percent state that Spanish is

there primary language. Sites that send their cytology to Quest laboratories will also be identified to allow for consistent cytology collection medium and processing.

## **Selection of Participants**

### *Inclusion Criteria*

#### Intervention arms:

We will identify Family PACT providers who meet the following inclusion criteria:

- Is located in one of the ten Southern California study counties
- Clinical care visits occurred to at least 200 women aged 21-29 years in FY 11/12
- Has a calculated average cytology interval of < 30 months (based on last 3 years)
- Cytology is sent to Quest laboratories

For comparison, we will select from the following:

- Is located in one of the ten Southern California study counties
- Clinical care visit occurred to at least 200 women aged 21-29 years in FY 11/12
- Has a calculated average cytology interval of < 30 months (based on last 3 years)
- Cytology is sent to Quest laboratories

## **STUDY METHODOLOGY**

### **Study Intervention**

#### *Choice of Comparators*

We will compare 2 different interventions arms that are designed to prevent overscreening and over treatment by increasing adherence to the new US cervical cancer screening guidelines<sup>33</sup> and the ASCCP guidelines for the management of abnormal cervical cancer screening tests and cancer precursors.<sup>36</sup> Specifically, the interventions will focus on lengthening cervical cancer screening intervals to every 3 years, decreasing colposcopy procedures for minimally abnormal cytology results and decreasing treatment of cervical precancerous lesions with a high rate of regression (i.e., cervical intraepithelial neoplasia grades 2 and 2/3).

The two arms will be:

- 1) Mobile application (APP)-based intervention for providers,
- 2) Mobile application (APP)-based intervention for providers PLUS patient-centered approach intervention (PCA).

The two arms will be compared to a comparison group (no intervention).

The APP-based intervention (APP) is for clinicians' mobile phones and will maneuver them through current guidelines (cervical cancer screening and management of abnormal cytology and histology) based on patient age and condition. This is the current ASCCP tool, which will be updated to include screening guidelines and risk assessment so the provider can better understand the risk associated with follow-up versus premature triage to colposcopy.

The patient-centered approach intervention (PCA) is oriented towards educating women about HPV and cervical cancer screening. The intervention will be provided to patients' when they check-in for a clinic appointment, and will interactively provide information designed to help them understand current guidelines for the frequency of cervical cancer screening and appropriate management for abnormal cytology and treatment options. It will allow them to assess the risks and benefits of screening intervals and of treatment choices.

Comparison sites will have no intervention.

This approach will allow us to examine what the additional benefit of educating women and providers would be over educating providers only. Our design also underscores downloading of mobile applications are passive and does not equate with knowledge of or use of the mobile application. Within the intervention arms, providers will be systematically educated on all the functions and capabilities of the mobile application and to ensure that the application is used consistently.

The comparison group is likely to include providers who have already downloaded and use the application. But this group would not have been systematically educated as to how to use the application, hence allowing us to examine the role of education around the integration of the mobile application into counseling.

### *Development of the PCA Intervention*

Four focus groups will be held both English and Spanish speaking, separately. With the assistance of NCCC and LCC, our patient stakeholders women aged 21-29 years of age will be identified for each focus group (See **Appendices A & B** for Focus Group Scripts). The focus groups will review the guidelines and their rationale and ask women what messages would be most appropriate and acceptable to the target population. Women with cancer, CIN and no abnormal cervical cytology will be targeted for inclusion whenever possible. Women who have never been screened for cervical cancer also will also be sought to participate. Issues that will be addressed include fears, concerns, and areas of uncertainty she may have around screening, and potential messages that could be used to address these issues. Thematic areas will focus on: cervical cancer screening intervals in young women under 30 years; natural history of HPV, follow-up of ASCUS and LSIL cytology by cytology only in women aged 21-24 years vs. immediate referral to colposcopy, follow-up of biopsy proven LSIL by cytology without treatment, follow-up of biopsy proven HSIL by colposcopy and cytology vs. immediate treatment, treatment options (cryotherapy vs. excisional therapy).

Transcriptions of the oral discussions of the focus groups will be taken and distributed to the group. Based on the transcriptions, we will develop a paper tool.

#### ***Themes within in the intervention include:***

- Defining what is a Pap smear
- Defining what is a cervix
- The relationship between HPV infections and Pap smear
- The natural history of HPV (clearance versus persistence) and its relationship to cervical cancer
- Perceived Importance of Pap smears
- The risk benefit ratio of overscreening
- The risk benefit ratio of overtreatment
- Understanding cervical cancer screening interval recommendation
- Understanding HPV testing recommendations
- Understanding how the new guidelines were established
- Understanding the new guidelines for abnormal cytology

Once the research and stakeholder team review the paper tool and agree to its flow and content, 5-10 women, with a history of normal cytology, no history of screening and abnormal cytology will be solicited through the stakeholders (NCC and LCC) as well as flyers (See **Appendices C & D**) at clinics and bus stops to participate in a cognitive interview (See **Appendices E & F**). Women will be walked through the paper tool and address clarity, cultural sensitivity, and appropriateness of messaging. All interviews will be recorded and transcribed. Both English and Spanish speaking women will be identified. Changes will be incorporated after each feedback (if time permits) and incorporated before the next interview. (See **Appendices G to J** for Final Paper tools)



### *Technology Design*

**Media:** A URL based app will be developed and tested. After each testing, notes will be taken by the SC and then reviewed by the team for clarity, flow, interest, and ease of use. NCCC and LCC will be asked to review and give feedback. Ten women will then be asked individually to review the URL and give feedback in a one to one setting. The URL website allows us to easily make changes over time as input is given.

**Userface design:** The media will be a combination of pictures, words, short videos and interactive buttons in order to engage and hold the attention of the woman.

The application will be developed using a responsive design approach—a website optimized for viewing on a tablet or phone allowing the app to be used on both iOS and Android devices as well as easily distributed later. The responsive design approach will allow the incorporation of videos and animation using HTML 5. During the study, the app will be distributed to clinics through a URL: <http://medschool2.ucsf.edu/preview/dots/site/>.

The application will be both unit and functionally tested to work in the targeted tablet devices and browsers identified by the study team. In addition, the study team will work with the identified clinics to ensure wireless coverage.

The tablet will not be set up to collect any data on individuals.

### *Final Product Development*

The final URL will be reviewed and edited by the team (research and stakeholders NCC and LCC) until the group agrees on all content, flow and messaging feedback. The application will allow women to choose English or Spanish language. Then they woman will be able to choose whether she is there because she had an abnormal Pap smear or not.

#### Content for cervical cancer screening (no current history of abnormal cytology)

- Introduction to Pap smears
- Description of normal anatomy including cervix, uterus, fallopian tubes
- How a Pap smear is obtained
- What Pap smears look for (abnormal cells)
- What is the connection between HPV (what is HPV) and Pap smear
- How common is HPV
- Risk of cervical cancer
- Importance of Pap smear
- When women should first get screened
- How often women should get screened
- Risks and Benefits to increased intervals
- Screening for women with HIV and other immunosuppressive disorder
- How women can protect themselves; through HPV vaccination, condom use, stop cigarette smoking and getting tested regularly for STIs
- Questions women might want to use to ask their provider

## Self-assessment Quiz (See **Appendices K & L**)

### Content for history of current abnormal cytology

Introduction to Pap smears

Description of normal anatomy including cervix, uterus, fallopian tubes

How a Pap smear is obtained

What Pap smears look for (abnormal cells)

What is the connection between HPV (what is HPV) and Pap smear

How common is HPV

Risk of cervical cancer

What is an abnormal Pap test

Relationship between abnormal Pap test and cervical cancer

What happens next if I have an abnormal Pap test

Description of colposcopy

Description of a biopsy

What happens after colposcopy

What type of procedures are available for treatment

Questions around partner treatment and transmission

How women can protect themselves; through HPV vaccination, condom use, stop cigarette smoking and getting tested regularly for STIs

Questions women might want to use to ask their provider

Self-assessment Quiz (See **Appendices K & L**)

### *Final Pilot Testing*

We will ask an additional 5-10 women recruited by NCCC, LCC and local women to participate in individual interviews to pilot test the program in a simulated clinical environment. Women who have had LSIL, HSIL, colposcopy with biopsy, and never screened will be solicited. The only introduction that will be given will be that similar to what will be given at the clinic sites. They will be asked to complete this education/self-assessment tool about cervical cancer screening and treatment options in accordance with their clinical history. These visits will be conducted by members of the research team and feedback sessions will be audio recorded. Immediately after using the intervention, the woman will complete a semi-structured interview that reviews her general reactions to the tool and her feedback and suggestions for specific components. Attention will be paid to the appropriateness of the information provided, both with respect to content and format, and the degree to which the tool addressed the common concerns women may have in each area. We will also explore whether the layout and navigation of the tool are accessible and clear. Specifically, we will ask whether she feels the tool helped in hearing the information and making decisions for cervical cancer screening intervals as well as treatment or follow-up. The study team will also debrief on the perceived influence of the tool on the potential clinical interaction with their provider. This information will be brought back again to the team and any modifications will be made to the intervention. Following completion of 4-5 interviews, the study team will meet and discuss changes to the tool based on the feedback and implement these changes. This process will be then be repeated in an iterative manner with 5 additional women if needed.

Final product will be an interactive, computerized, educational tool for cervical cancer screening and management of abnormal cytology and histology which will be informed by patients' preferences and experiences of cervical cancer screening, colposcopy, biopsy and treatment as well as by the medical expertise of guideline experts. This tool will be designed to facilitate the counseling interaction by providing the patient with information about her options and assisting her in identifying her preferences and areas of uncertainty and is intended to assist the patient in determining important areas for discussion during the visit.

The final product will be approved by NCC, ASCCP, LCC and all investigators. ACOG (Committee on Adolescent and young adult) will be asked to review for their input.

### *Development of the Mobile Application Based Intervention for Providers*

Currently, the ASCCP has designed a mobile application for the management of abnormal cytology and histology guidelines based on the 2006 management of abnormal cytology and histology guidelines and the recently released updated guidelines: 2012 Updated Consensus Guidelines for the management of abnormal cervical cancer screening tests and cancer Precursors.<sup>12,13,36</sup> The mobile app can be purchased for both iPhones through the Apple store and Androids through Google Play. Both the iPhone and Android version of the App will be updated with PCORI support to help providers assess risk as well as provide guidelines for screening. Risk assessments will help providers understand the need to refer to colposcopy versus to watch observantly and to treat versus watch observantly. This effort will also involve National Cancer Institute. For example, young women with LSIL on cytology is a low risk for CIN 2/3, hence the management recommended is repeat cytology in one year not colposcopy. The risk associated with the development of CIN 2/3 is given under these circumstances. The American Cancer Society screening guidelines will also be added. For this application, there is no data exchange nor data collection – it will simply be a decision tool for the doctor.

## **Study Implementation Procedures**

### *Study Enrollment Procedures*

#### Contacting sites:

A letter will be sent to all clinic administrators of eligible sites explaining the study. A follow-up phone call will occur one week later. We will explain the study over the phone and those interested and agree to participate will be identified as clinics eligible to randomize to an intervention arm. If more than 14 sites agree to participate, we will let the sites know that they may not be asked to participate. If more than 14 sites agree, the 14 sites will be chosen based on identifying a balance of private and public clinics so that the average number of women aged 21-29 years is 500, and a relative geographic distribution among the 10 counties and that both English and Spanish languages are well represented according to the county's proportion of Hispanics.

Of those eligible for the comparison sites, we will identify sites using the eligibility criteria, and randomly identify 7 sites but with matching for private and public clinics and relative size of

practice which may range from 200 to over 1000 clients. There will be no contact with these sites since the outcomes data will be monitored from the Family PACT claims database.

Randomization:

Block randomization of clinics to one of the two arms will be performed by the biostatistical group at UCLA.

Site set up:

Dr. Moscicki and the PC will visit all 14 identified clinics sites to meet with staff, identify a key contact person for the site, discuss flow issues, and discuss the protocol.

***For clinics randomized to APP-based intervention alone (arm 1):***

We will ask each of the providers to download the ASCCP application prior to the in-service or at the beginning of the in-service. We will meet with each of providers in the practice in person for a 30-minute session to introduce them to and provide basic guidance to the ASCCP mobile application. This will include showing them the screening guidelines on the application, and using several scenarios as examples to practice its use. These will all focus on women under 30 years of age. If any new providers are hired during the period, the PC will come out to provide them with orientation to the web based application. It is expected that some of the providers will already have the APP. We will ask them to participate in the in-service as well.

***For clinics randomized to APP with PCA-based intervention (arm 2):***

In addition to the training described above for the providers, we will work with clinic staff randomized to this arm to optimize implementation of the patient-directed application. First, staff will be introduced to the goals of the application, and will be taken through it in an interactive manner, allowing for questions and answers. The PC will train staff in using the website, how to connect to and open the URL, and begin the application. The intervention is expected to be easy to use but in case the clients have questions, the staff will be trained.

For implementation, we will work interactively with the clinic staff to make sure the tablet is provided as part of normal clinic flow. This may involve the front desk or nursing visit during vital signs depending on the clinic. The SC will work closely with the site to make sure all age appropriate (21-29 years) are given a tablet at the time of their visit. Instruction will be given how to interact with the patients regarding assessing their interest and giving them the website information for their own devices or use of the tablet we provide the clinics. The tablet will be either held with the staff (encased in a large case in order to deter theft) or will be locked to a specific site in the waiting room, depending on the configuration of the clinic. For those sites with no Wi-Fi connectivity, we will purchase a monthly Wi-Fi subscription for the tablet.

Adherence:

Although we will not have site-specific data, we will be able to see how many times the PCA has been viewed.

### Comparison Arm:

No site set up will be performed with comparison groups.

### *Quality Assurance*

The PC will identify a point of contact for each intervention site with whom to maintain monthly contact via email/telephone, depending on the type of interaction the site staff requests to ensure that the tablet is functional and remind them to use it in clinic flow. We will ask approximately how many times a week the tablet is being used, how many women refused (in the 21-29 year old), how many women were not offered the tablet. We initially will make weekly calls/emails. After the first month, we will make monthly contact.

The PC will visit all participating intervention arm clinics 2-3 times a year. At that time the PC will ensure that the interventions are in place -- tablets are being functional and are being offered to all age-appropriate women attending the clinic, and all provider phones have a functional mobile application. In addition, to collecting satisfaction surveys, the PC will also collect data on any potential factors that may bias or contaminate an arm (i.e., webinars attended by staff on cervical cancer screening, mobile apps present on the other intervention arms, among others.) using the Quality Assurance Survey (See **Appendix M**). This will be collected at the end of the first and second years. Sites will be reimbursed \$1,000 each a year for their participation in the Quality Assurance Project.

### *Satisfaction Survey*

The PC will attend all the clinics 2-3 times a year. At this time, women attending the clinic and complete the tablet intervention will be asked, after consenting, to complete a satisfaction survey (See **Appendix N**) at the end of the visit that will ask the patients, age, cytology diagnosis, and whether the tool was useful, easy to use and did they feel it gave them adequate information regarding cervical cancer screening guidelines and treatment options. Forty women from each of the sites (200 for each arm) will be solicited years 2 and 3.

### *Progress Review*

All stakeholders will convene twice a year (month 7 and 12) and review the progress, issues, problems and feedback from the clinic sites, satisfaction survey and interim and final outcomes data. When necessary, changes to the protocol or interventions will occur if deemed appropriate by the group.

### **Sample Size Estimates and Power Calculations**

The database for FY 2010/11 shows that 386 clinics fit the criteria with 89 sites available for arms 1-2 and 297 available for the comparison group. The mean number of female clients aged 21-29 years seen at the eligible clinics was 560 and the mean number of cytology specimens, colposcopic examinations and LEEP/cryoprocures for this age group was 297, 40, and 4, respectively. In 2012, the mean cytology interval was 19 months. Very few clinics had an interval >30 months. There were no differences for any of the above variables between those

sites eligible for intervention and those for comparison. These numbers have not changed significantly in the past 2 years and will be updated for the baseline assessment.

After enrolling 7 sites into each arm, we estimate that we would have approximately 2800-3500 women aged 21-29 years in each arm. For each arm, baseline cytology rate in this age group would be approximately 50%, rate of colposcopy procedures for those who had cytology would be 13%, and rate of LEEP/cryotherapy procedures for those referred to colposcopy would be 10%.

Sample size calculations for the primary endpoint (rate of cytology testing) are based on a pairwise comparison of observed changes from baseline in clinic-specific three-month testing rates between intervention study arms (APP or APP+PCA) and the control arm, using a t-test adjusted for clustering on the clinic level. The baseline rate in control clinics is assumed to be approximately 50%, consistent with the preliminary data presented above. Assuming that there will be no observed change in rates for control clinics during the testing period, our expected sample size of 9030 (i.e. 3010 per arm, seven clinics per arm, and an average of 430 women per clinic) will be sufficient to provide 90% power to detect a between-arm difference as small as 16% as significant. This calculation assumes a quite conservative value for the intracluster correlation of outcomes within clinics of 0.07, and is based on a 1% significance level to account for the fact that there will be two pairwise comparisons with the control arm (i.e. one per intervention arm). Accounting for as much as 10% missing data on testing rates, we will still retain more than 90% power to detect differences of this magnitude or larger between arms as significant at the 5% level. We should also retain adequate power to conduct additional sensitivity analyses investigating the possible confounding influence of clinic-level descriptors (e.g. race/ethnicity and age distribution) on observed results. Finally, we note that our proposed analysis that will account for within-clinic paired observation of outcome rates and adjust for baseline covariates will likely yield more power than the conservative estimates made above. Although the study is not powered to detect significant differences between intervention groups, a similar calculation for the comparison between the APP and APP+PCA groups indicates that we retain at least 70% power to detect a difference in observed changes in testing rates as small as 15% as significant at the 5% level.

Parallel calculations for the secondary colposcopy outcome also are based on between-arm comparison of changes in three-month colposcopy rates from baseline levels, and assume that approximately 50% of women will receive cytology at baseline and follow-up in the control group, and that colposcopy rates will also remain unchanged at 13%. We also assume that the intervention-related reduction in cytology will result in approximately 20% fewer women eligible for colposcopy at follow-up. Based on similar assumptions about intracluster correlation and loss to follow-up, results indicate that with the planned total sample size of 9030, we will retain at least 80% power to detect an intervention-related reduction in colposcopy rate as small as 8% at the 5% (one-sided) significance level. Due to our conservative assumptions, we should have sufficient power to detect even smaller intervention-related effects in analyses adjusting for baseline characteristics.

We did not perform calculations for the testing interval length and LEEP outcomes because of the lack of preliminary data on their potential variability within and between clinics.

## ANALYTIC METHODS

### Research Question

Does provision of patient and provider educational materials increase adherence to cervical cancer screening guidelines (increase in screening interval and decrease in diagnostic and excisional procedures) in women under age 30?

### Choice of Outcomes

Family PACT claims data will be used to examine by age, the number of and average interval between cytology specimens, and the number of cervical procedures. However, we hypothesize that the group with both interventions (physician plus patient interventions) will be more successful in guideline adherence than physician interventions alone or the comparison group (no intervention).

### Missing Data

Missing data may arise at several points in the study. Clinicians have six months to submit a claim for reimbursement after the last date of service. The claims data are 90% complete at the last date of service and 99% after six months of the last date of service. We will feel confident that we can conduct the statistical analysis in years 1 (pre-intervention) and 3 (post-intervention) with a 90% complete dataset but will rerun the models in year 2 (interim data analysis) to confirm the results with the 99% complete dataset for pre-intervention and will rerun the end of study results at 6 months post end of study. Patient information may be missing on the examination or intake form or from the patient satisfaction survey or patients may drop out or be lost to follow-up in the study. The randomness of this information will be examined to ensure that its missing-ness is not related to any patient, clinic, or intervention arm factors. In addition to this, lab results may be contaminated or lost entirely. The pattern of unusable lab results will be analyzed to identify any clinic or intervention arm bias. Reasons for missing data will be collected and tabulated.

### Data Analyses

Outcomes to be evaluated within and between intervention arms are based on the specific research aims:

**a) Decrease the rate of cervical cytology testing among women ages 21-29 years of age**

**Pre:** Rate of women 21-29 years of age who received cervical cytology tests over total number of women 21-29 years of age in quarter (3 months) before start of intervention

**Post:** Rate of women 21-29 years of age who received cervical cytology tests over total number of women 21-29 years of age in months 3-6, 9-12, and 15-18 after intervention started

**b) To increase average length of cervical cytology testing among women under 30 years of age**

**Pre:** cervical cytology test interval among women who received two CC tests from same provider (analysis limited to providers who have been in program at least 36 months)

**Post:** cervical cytology test interval among women who received their second CC test 3-15 months after the intervention started.

**c)** To decrease the number of LEEP and cryotherapy procedures in women under 30 years of age with abnormal cytology.

**Pre:** Rate of women 21-29 years of age who receive LEEP or cryotherapy over total number of women 21-29 years of age in quarter before intervention started.

**Post:** Rate of women 21-29 years of age who receive colposcopy or LEEP or cryotherapy over total number of women 21-29 years of age in 3-6, 9-12, and 15-18 months after intervention started.

**d)** To decrease the number of colposcopy procedures in women 21-24 years of age with abnormal cytology.

**Pre:** Rate of women 21-24 years of age who receive colposcopy over total number of women 21-24 years in quarter before intervention started.

**Post:** Rate of women 21-24 years who receive colposcopy over total number of women 21-24 years of age in 3-6, 9-12, and 15-18 months after intervention started.

The primary outcome measure will compare the observed within-clinic changes in cervical cytology testing rates between intervention and comparison groups using a t-test accounting for clinic-level clustering. We will use the same approach to test differences between each of the APP and APP + PCA and the comparison groups. Tests will be adjusted for multiple comparisons. Secondary endpoints include examining the interval between tests for women who received two cervical cytology tests from the same provider and the decrease in the number (and percent) of women receiving colposcopy procedures and LEEP or cryotherapy procedures. These will be analyzed using a similar approach as adopted for the primary endpoint. Patient satisfaction surveys will be administered to all women evaluated and compared between interventions and the controls. Because most available data is on the clinic level, we will have limited opportunities to analyze patient-level data. However we will be able to conduct supplementary analyses to investigate the possible impacts of between-arm imbalances in clinic level characteristics such as racial/ethnic composition, age distribution, descriptors of lab procedures, additional app or educational materials that are not part of the assigned intervention, and cervical cancer screening educational activities. Prior to starting the intervention and during the study, administrators and physicians at each clinic site will be asked about possible confounding variables at their clinic.

#### *Sensitivity and Heterogeneity of Treatment Effect:*

Each intervention group and the control group will be examined for its sensitivity and heterogeneity by using a jack-knife technique computing the intervention effect leaving out each of the clinics consecutively. The variability of the results of these analyses within intervention will be compared to the overall effect to examine how sensitive the results are to each clinic. Within each clinic, patients with some missing data will be included and then excluded from the summary analyses of that clinic and intervention to examine sensitivity of the patient results to



the overall clinic and intervention effects. These analyses will be tabulated and reported by clinic, by intervention, and overall.

## PROTECTION OF HUMAN SUBJECTS

Human subjects protection will be of utmost priority throughout the research study. Study personnel will strictly adhere to policies and regulations as defined and outlined by the Institutional Review Board (IRB) for Protection of Human Subjects of the University of California, San Francisco (UCSF) (Award Number: A122561) and the University of California, Los Angeles (UCLA) (IRB Application still under review as of 4/29/15).

### Potential Risks

Focus groups, interviews and mock pilot testing: Potential risks are low in all three formats. Inadvertent disclosure of patient's condition such as having cervical cancer may cause embarrassment or psychological distress in the focus groups. For the focus groups and interviews, discussion about procedures that previously caused distress may invoke stress. Since these women are volunteers and it will be explained to them ahead of time, it is likely that these risks are extremely low. Women who will try the mock intervention are not likely to have any risks unless as above, it induces stress given a past situation.

*Randomized Intervention Trial:* Risks for participation are low. It is possible that completing the tablet intervention will induce anxiety, however, input from the community stakeholders and patients during the development of the app should keep this to an extremely rare event, if ever. Women do not have to complete the tablet intervention and they can stop it any time. The tablet will be voluntary at the clinic sites. No PHI will be collected from the tablets on the women for this study nor shared with investigators. Data from the tablets is not stored anywhere including the risk assessment. It will be deleted immediately after clients complete the survey.

*Patient Satisfaction Survey:* Risks for participation are low to none. Patients will be asked about age and condition but no personal identifiers will be collected. Information about ease of tablet use will be asked as well as whether the tablet was informative and helpful.

*Protections Against Risk:* For focus groups, women will be asked prior to consenting if they are comfortable talking about their condition (cervical cancer, dysplasia). If they are not, then they will be asked not to disclose any time during the focus groups. All tape-recorded data will be immediately brought back in a locked carrying case to UCSF where it will be stored in a locked cabinet until used for feedback. Some of the discussions may reveal certain sexual behaviors. We will instruct the focus groups that everything said at the focus group is considered confidential and we ask them not to repeat any information shared at the focus group. If anyone feels uncomfortable we will excuse them. In addition, we will make sure that they feel that they do not need to respond to ours or others questions. No individual information will be identified or recorded. Individual interviews will be asked similar questions and tape recording will be handled similarly. If at any time a women appears uncomfortable, we will stop the interview.

*Individual interview and mock intervention:* First, beta form for the intervention will be submitted to the UCSF CHR for final approval prior to testing the version. Upon approval, women who will be asked to perform the mock interventions will be instructed that if they feel at any time uncomfortable with the intervention, they can stop at any time. Also if they have any questions during the intervention, they can ask the study coordinator. Tape recordings will be handled similar as above.

The electronic data sets are protected with a password and stored on a secure network. The servers containing the data are kept in a locked office with limited access inside of a locked suite at the DHCS in Sacramento. All UCSF personnel working with the data have signed confidentiality agreements and completed HIPAA training courses.

### Benefits to Subjects

*Focus groups/interview/mock pilot testing:* no benefits will occur for participating in the study except that the subjects may gain important information regarding cervical cancer screening. Risks to the subjects are low. Inadvertent disclosure of HPV status or cervical cancer status may occur which could cause distress.

*Randomized trial clinics:* Risk to the women is very low since the tablets are informational. In addition, the final intervention will be submitted to the UCSF CHR and UCLA IRB for final approval before moving onto the randomized trial. Women will not be randomized only clinics. Women may benefit since they would have increased education and more satisfaction having knowledge about cervical cancer screening guidelines. Patient may benefit if screening guidelines are adhered to by the provider.

*Patient Satisfaction survey:* No benefit will occur the women for completing the survey.

### Benefits to Society:

The knowledge from the focus groups and interviews will serve the development of the patient intervention tool. This in turn may increase adherence to the US Cervical Cancer Screening (CCS) guidelines and management of abnormal cytology. This in turn would result in decrease invasive procedures for young women. The study may give us insight in to how to assist provider and patients to adhere to the US CCS guidelines. The risks for participation in the focus groups and interviews are low. Information from the trial may give us intervention tools that increase adherence to guidelines by both providers and patients.

### Explain why the risks to subjects are reasonable:

Risks are very low and will hopefully benefit women at large from unnecessary intervention.

### Compensation for Participation:

Participants for the one-hour focus groups, interview, and pilot testing will receive \$50. Participants of the Patient satisfaction Survey will receive a \$10 gift card. Participants and their insurance will not be charged for any study procedures.

(See **Appendices O to T** for consent forms for focus groups interviews, cognitive interviews, and satisfaction surveys)

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