Short Research Summary

Study Title:

FAMILY HEALTH MINISTRIES' Non-Inferiority Evaluation of the *"CerviScope"*

Principal Investigator:

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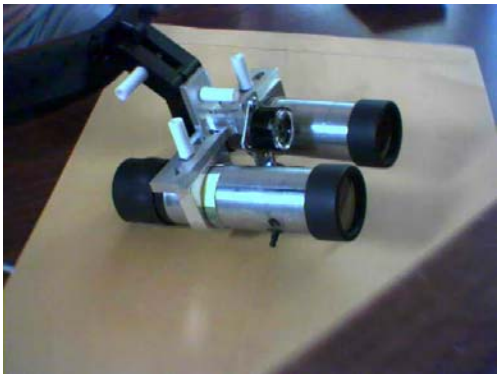
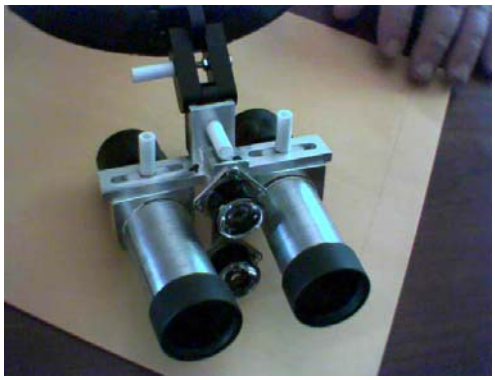
Contents

Purpose of the study

The purpose of this study is to compare the performance of a portable colposcope, called the "CerviScope", to a standard colposcope and to VIA in the hands of a trained colposcopist who is working in a resource-poor country where most women have never had access to cervical screening.

Background, Significance & Preliminary Data

The morbidity and mortality of cervical cancer is concentrated disproportionately in resource-poor nations where 80% of new cases arise annually. Although effective strategies to prevent cervical cancer exist, they are not widely practiced in many countries because there are too many obstacles for women to access care or complete the multiple visits required for diagnosis and treatment. Also, when resource-poor countries begin to offer cervical cancer prevention programs, they often import strategies from countries like the United States, where routine screening is widely available and practiced. These strategies, which place a higher value on specificity than sensitivity, are not as effective in resource-poor countries where the prevalence of cervical cancer is high and large populations of women can not being screened multiple times during the treatable stages of the disease. Therefore, there is a search in many countries around the world for cervical cancer prevention strategies that place a higher emphasis on sensitivity than specificity as a way of reaching more women with fewer exams until resources become more available.

Strategies that start by inspecting the cervix visually are more sensitive at picking up HPV-related disease than cytology-based screening programs. (Table 1, page 9) Visual inspection also has the advantage of being less expensive and it does not require the expertise of a cytology laboratory.

Colposcopy: Data collected by Family Health Ministries, Inc. in the Leogane Commune of Haiti between 2001 and 2005 using colposcopy as a primary visualization screening strategy (Table 2, page 9) demonstrated that ~40% of the disease (≥CIN II) detected by a blinded colposcopic examination would have been missed if conventional Pap smears had been used as the primary screening strategy, due to know issues with cytology as well as the high prevalence of obscuring inflammation (Table 3, page 9). In Leogane, some practitioners are beginning to consider

eliminating standard cervical cytology from their standard screening protocol after seeing this data knowing that 1) approximately 1/3 of the women who request screening are not able to return for all of their follow up visits and 2) some that do often don't have the money to pay the pathologist. Liquid-based cytology techniques may be an excellent alternative to conventional cytology if they weren't prohibitively expensive in this setting.
VIA: Visual inspection without magnification (VIA) is another strategy being embraced in many countries because a colposcope is not needed and some studies have reported that treatments based on looking at the cervix with the naked eye can reduce the incidence of disease in unscreened communities with a high incidence of cervical cancer. VIA was considered in Haiti but the physicians were reluctant to implement it because of the perception that VIA represented substandard care. However, Haitian healthcare providers were willing to consider a screening strategy for cervical dysplasia that was based on colposcopy findings, which they believed was more consistent with accepted international standards of care.

One drawback to screening with colposcopy in resource-poor countries is that standard colposcopes are expensive, heavy and electricity-dependent. This problem has been the primary motivation for initiating VIA programs. Family Health Ministries, Inc. has been investigating another possible solution to this problem by developing an inexpensive, lightweight, battery-powered, portable colposcope over the last 10 years. (Figure 1, page 10) The initial prototypes of the portable colposcope performed well in a field test compared to a standard colposcope.[1] However, it was not utilized because it was perceived as being was too heavy on the bridge of the user's nose. This year, FHM's portable colposcope concept won the CURES competition at Duke University, which is providing support to professionally design, build and manufacture a modified lighter alpha version of the portable colposcope, which is not being called the CerviScope. This award is restricted to design and manufacture support and can not be used to support this trial. Because of the increasingly complex biomedical engineering aspects of this project, Family Health Ministries decided that it made sense to form a second 501c3, non-profit corporation called ImaGyn (& pronounced 'imagine'), under the leadership of Theo Tam. In partnership, Imagyn (www.imagynation.com) will oversee the design and manufacture the "CerviScope" while Family Health Ministries, Inc. will be in charge of the field testing and training health care providers in its use. If this non-inferiority trial is successful, the data gathered will be used to build a beta-version of the "CerviScope" later next year.

Design & procedures

PRIMARY OBJECTIVE: CerviScope vs. Standard Colposcope

The primary objective of this protocol is to compare the performance of a portable colposcope called the "CerviScope" to a standard colposcope in the hands of a trained colposcopist who is working in a resource-poor country where most women have never had access to cervical screening.

The performance of the "CerviScope" will be evaluated primarily by comparing the "CerviScope" to a standard colposcope with regard to its ability to…

1. …visualize lesions on the uterine cervix. (Figure 2, page 10)

    a. …discern characteristic vascular patterns of cervical lesions.
    (Figure 3, page 10)

    b. …convey information that will help the colposcopist identify cervical lesions that represent HPV-related disease?
    (Figure 4, page 10)

The performance of the "CerviScope" will also be assessed by comparing the "diagnostic impression" of each instrument to the Gold standard, i.e. the cervical biopsy results.
(Figure 5 & 6, page 11)

Because of a concern from a previous study that visualization techniques may be missing a significant amount of HPV-related disease, blinded cervical biopsies will be taken from any quadrant of uterine cervix that does not exhibit a lesion. For more information on this, see the background & significance section. In addition, endocervical curettages will be done if the entire squamocolumnar junction is not visible.

SECONDARY OBJECTIVE #1

A secondary objective of this protocol is to compare the performance of VIA to the standard colposcope in the hands of a trained colposcopist (also trained in VIA) and who is working with a largely unscreened population of women in low resource communities.

The performance of the VIA will be measured by comparing VIA to a standard colposcope with regard to its ability to…

1. …visualize lesions on the uterine cervix. (Figure 7, page 12)

    a. …discern characteristic vascular patterns within cervical lesions.
    (Figure 8, page 12)

    b. …convey information that will help the colposcopist identify cervical lesions that represent HPV-related disease?
    (Figure 9, page 12)

The performance of VIA will also be assessed by comparing the "diagnostic impression" to the Gold standard, i.e. the cervical biopsy results.
(Figure 10, page 12)

SECONDARY OBJECTIVE #2

Another secondary objective of this protocol is to compare the performance of VIA to the "CerviScope" in the hands of a trained colposcopist (also trained in VIA) and who is working with a largely unscreened population of women in low resource communities.

The performance of the VIA will be also be measured by comparing VIA to the “CerviScope” with regard to its ability to…

1. …visualize lesions on the uterine cervix. (Figure 11, page 13)

    a. …discern characteristics vascular patterns within cervical lesions. (Figure 12, page 13)

    b. …convey information that will help the colposcopist identify cervical lesions that represent HPV-related disease? (Figure 13, page 13)

We will ask for feedback from each user to determine what they liked / didn’t like about the design of the “CerviScope”. We want to get ideas from the users about how to improve the design of the instrument before we manufacture the final beta-version. (see Feedback page 14)

Inclusion (Exclusion) Criteria:

All subjects must…

1. …have been sexually activity for more than 5 years
2. …be between the ages of 30 – 60
3. …be more than a week past their last pelvic examination
4. …have no active vaginal bleeding

This study involves doing three serial visual examinations of the cervix of by one observer after painting the cervix with 4% acetic acid.

VIA:

- The 1st exam will be conducted using VIA without magnification.
- A colposcopy assistant must completely fill out the VIA datasheet before the colposcopist moves on to look at the cervix with the CerviScope.
- The colposcopist will note whether the entire squamocolumnar junction is visible.

The 2nd and 3rd exams will be conducted with the CerviScope and the standard colposcope. The order of these two examinations will be randomly assigned.

CerviScope:

- After this examination is completed the colposcopy assistant must completely fill out the CerviScope datasheet before the colposcopist moves on to the next step up the protocol.

Standard Colposcope

- The 3rd exam will be conducted using the standard colposcope.
- After this examination is completed the colposcopy assistant must completely fill out the standard colposcopy datasheet before the colposcopist moves on to the next step of the protocol.

Biopsies

- All lesions seen by any of the three visualization methods will be biopsied.
- A blinded biopsy will be taken at the squamocolumnar junction of each quadrant that appears normal by all three visualization methods.

Definition of clinical and research activities

Clinical Activities

1. Vaginal speculum placement
2. Standard colposcopy & cervical biopsies of all suspicious lesions

Research Activities

1. Visual inspection of the cervix without magnification & recording findings
2. Inspection of the cervix with the “CerviScope” & recording findings
3. Cervical biopsies in any quadrant of the cervix that appears normal by all three visualization methods

Risk/benefit assessment

Potential Risks:

1. The speculum will be in the subject's vagina for 1 - 3 minutes longer than a normal colposcopic examination to allow the physician to examine and record his/her findings from all three examinations.
2. All subjects will receive at least four cervical biopsies even if no lesions are visualized on their cervix. The biopsies are likely to be painful and to cause bleeding. In rare cases they could result in an infection. Some vaginal bleeding and a small amount of dark brown discharge are normal for about 1 to 2 weeks. In order to minimize the chances of an infection, subject will be advised to avoid sexual intercourse and douching for 1 week and to return to the clinic for evaluation if they develop heavy bleeding, fever or a persistent foul-smelling vaginal discharge.

Potential Benefits:

1. Given the preliminary data gathered in Leogane, it is possible that some of the random biopsies will identify advanced treatable HPV-related lesion that would have been missed with either cytology or colposcopy.

I Investigational Device

The "CerviScope" has not been approved in the United States by the Food and Drug Administration. This device will be worn by the examiner and will never come into direct contact with research subjects. The light emitted by the device is comparable to that emitted by a flashlight. All research subjects will be screened with a standard colposcope.

The device used in this study is a diagnostic device that meets all four of the following criteria for exemption from FDA IDE requirements: the testing…

- …is non-invasive; i
- …does not require invasive sampling presenting significant risk;
- …does not introduce energy into a subject; and
- …is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic device or procedure (21 CFR 812.2(c)(3)).

- **Study Sites**
- With this application, we are proposing to conduct this study at the FHM cervical cancer prevention program in Leogane, Haiti. Dr. David Walmer will be the Principal Investigator for Family Health Ministries and Dr. Delson Merisier will be the co-investigators will be in Leogane, Haiti.

- At this time, we anticipate that we will come back to the IRB with a request to amend this study to include study sites at Moi Univesity in Eldoret, Kenya and Aga Khan University in Karachi, Pakistan. We are not including that plan as part of this application because the details of funding and leadership are still being worked out. At this time we are in

discussion with Dr. Jeffrey Wilkinson about doing the trial in Eldoret and Dr. Jokhio Hakeem at Aga Khan in Karachi. Each site that is added will individually fulfill the requirements of the Duke IRB and the de-identified data will be kept at the offices of Family Health Ministries, Inc. located at 2344 Operations Drive, Suite 201, Durham, NC 27705.

- **Subject identification, recruitment, and compensation**
- In Leogane, the women for this study will be recruited largely by word of mouth. We recently conducted a Qiagen-sponsored investigation of the FastHPV assay in Leogane and had no problem recruiting about 600 women that met study criteria in 6 weeks. The women in Haiti are eager to be screened and come from areas where the incidence of dysplasia and cancer are high. Recently, we created an educational song about cervical caner in Haiti that informs women about our program in Leogane. This song will begin to air on the radio within the next few months. The women will not be compensated for participating in the study.

- **Subject competency**
- Only subjects who are competent to consent to the research will be recruited.

- **Consenting subjects**
- An IRB approved consent form will be written in the local language and translated forwards and backwards & compared for consistency. Literate subjects will read the consents and illiterate subjects will have the consent read to them. A member of each study team will be immediately available to witness the consent process and answer any questions. If the subject agrees to participate in the study, the witness and the research subject will both sign the consent. A copy of the consent will be provided to the subject. Only data collected by an IRB approved consent form will be used in the analyses for the study. The study will also be approved by a local IRB.

- **Costs to the subject**
- Haiti: In Leogane, Family Health Ministries supplements the costs of all clinical examinations as well as the processing and reading of the biopsies. In Haiti, the cultural norm is for all individuals to pay at least a nominal fee for any services that they receive. We will not change to fees that the clinic charges for this study.

- If additional sites are recruited, this information will be provided for each site.

- **Data storage, confidentiality, analysis & monitoring**
- Each research subject will receive a study number and the data collected at each site will be stripped of identifiers before it is sent to Family Health Ministries. A key linking the study number to each research site will be kept in a confidential location at the local clinic.

- **Statistical Considerations**
- <u>Study design relevant to calculating study sample size</u>
- Each woman will contribute up to four lesions in the study. A gynecologist with training in colposcopy will apply 4% acetic acid to the subject's cervix and examine it using 1) his / her

naked eye (VIA), 2) a new portable colposcope (CerviScope) and 3) a standard colposcope. The examination by each method (naked eye, standard colposcope, portable colposcope) will be recorded as positive (suspicious for dysplasia or cancer) or negative (not suspicious, i.e. inflammation or normal) for each lesion. The gold standard will be the final pathology of the lesion.

- In order to demonstrate non-inferiority of the CerviScope, i.e. not missing disease that the colposcope would identify, the study requires 125 women with positive pathology. Assuming a 20% of prevalence of cervical lesions, which is consistent with preliminary data in Haiti, the study will accrue a total of 625 women. This study could be done in less than 1 year at the site in Haiti where approximately 1200 women are currently being screened per year.

- **Statistical Analysis**
- The statistical analysis for this study will be conducted by Dr. Sin-Ho Jung.
- The primary objective of this study is to test if the sensitivity of the portable colposcope is non-inferior to that of the standard colposcope. Let p_1 and p_2 denote the sensitivities of the standard colposcope and the portable colposcope, respectively. Assuming that each woman contributes one lesion, a sample size of N=125 women with positive pathology will guarantee 85% power by non-inferior testing for H_0: $p_1 - p_2 \geq 0.05$ vs. H_a: $p_1 - p_2 \leq 0.01$ using (one-sided) α=0.05. Note that the readings by portable colposcope and standard colposcope are correlated for each woman. This sample size is calculated using the exact binomial distribution under the assumption that most of the positive readings by portable colposcope will be also positive by standard colposcope. Let, for each woman, X_1 and X_2 denote the readings by portable colposcope and standard colposcope, respectively, taking 1 if + and 0 if -. Then, under the assumption, $Y=X_1-X_2$ is a Bernoulli random variable with P(Y=1)=0.05 under H_0. Note that the difference between two paired sensitivities is so small that the paired two-sample t-test based on the asymptotic normality may not work. Since each woman will contribute up to four lesions, the final testing based on the clustered binary data (e.g. Jung and Ahn, 2000) will have a higher power.
- A secondary objective of the study is to compare the sensitivity between naked eyes and portable colposcope. From the literature, the sensitivity of naked eyes is reported as 20% to 60%. Under the same assumption as above, N=125 positive cases will provide almost 100% power to compare a sensitivity of 60% for naked eyes with a sensitivity of 80% for portable colposcope using two-sided α=0.05.

McNemar test will be conducted to see if the portable colposcope tends to miss diseased lesions more often than the standard colposcope. The McNemar test will be adjusted for clustered binary data too.

References

1. Walmer DK, Merisier D, Littman E, Rodriguez G, Venero N, Henderson M, Katz D, Edwards R. Portable colposcopy in low-resource settings. Journal of Acquired Immune Deficiency Syndromes 37(3):S167-170, 2004.

2. Jung SH and Ahn C. Estimation of response probability in correlated binary data: A new approach. Drug Information Journal 2000; 34:599-604.

Appendix: Tables & Figures

Table 1
Diagnostic Accuracy Analyses of Conventional Cervical Cytology and Colposcopy as Primary Screening Tools for Cervical Dysplasia in Leogane, Haiti 2001-2005

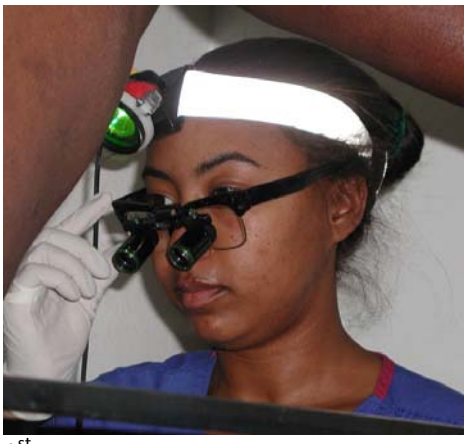
	Prevalence	Sensitivity	Specificity	PPV	NPV
Cytology					
≥ CIN I	41.9 %	68.7%	96.5%	93.4%	81.0%
Colposcopy					
≥ CIN I	48.0%	96.2%	53.9%	65.8%	93.9%

Table 2
Correlation of dysplasia on Pap smear with blinded colposcopically-directed biopsies.

	Pap (Dysplasia)					
Worst Biopsy Result	No dysplasia	CIN I	CIN II	CIN III	cancer	Grand Total
Normal	10					10
chronic cervicitis	45	2				47
HPV change	56	2				58
Mild dysplasia	10	9				19
moderate dysplasia	**2**		1			**3**
severe dysplasia	**4**	2	1	3		**10**
CIS	**1**					**1**
microinvasive cancer	**3**	3	2	1	2	**11**
Treatable disease ≥CIN II	**10**					**25**
Cancer	5	1		2	30	38
Grand Total	136	19	4	6	32	197

Table 3
Correlation of dysplasia with the degree of inflammation on Pap smears

	Conventional Pap (Dysplasia)					
Pap (Inflammation)	no dysplasia	CIN I	CIN II	CIN III	cancer	Grand Total
≤ mild inflammation	135	14	5	6	32	192
≥ moderate inflammation	1088	5				1093
Grand Total	1233	19	5	6	32	1295



1st prototype

2nd prototype

current working prototype

Figure 1

		Standard Colposcope	
		No lesion seen	Lesions seen
CerviScope	No lesion seen		
	Lesions seen		

Figure 2

		Standard Colposcope		
		No lesion seen	Non-suspicious lesion	Suspicious lesion
CerviScope	No lesion seen			
	Non-suspicious lesion			
	Suspicious lesion			

Figure 3

		Standard Colposcope Impression			
		White Epithelium	Punctation	Mosaiciam	Atypical Vessels
CerviScope Impression	White Epithelium				
	Punctation				
	Mosaicism				
	Atypical Vessels				

Figure 4

		Pathology Report from Cervical Biopsy				
		Normal	Inflammation	CIN I	CIN II - CIS	Cancer
CerviScope Impression	Normal					
	Inflammation					
	Dysplasia					
	Cancer					

Figure 5

		Pathology Report from Cervical Biopsy				
		Normal	Inflammation	CIN I	CIN II - CIS	Cancer
Colposcope Impression	Normal					
	Inflammation					
	Dysplasia					
	Cancer					

Figure 6

		Standard Colposcope	
		No lesion seen	Lesion seen
VIA	No Lesion seen		
	Lesion seen		

Figure 7

		Standard Colposcope		
		No lesion seen	Non-suspicious lesion	Suspicious lesion
VIA	No lesion seen			
	Non-suspicious lesion			
	Suspicious lesion			

Figure 8

		Standard Colposcope Impression			
		White Epithelium	Punctation	Mosaiciam	Atypical Vessels
VIA Impression	White Epithelium				
	Punctation				
	Mosaicism				
	Atypical Vessels				

Figure 9

		Pathology Report from Cervical Biopsy				
		Normal	Inflammation	CIN I	CIN II - CIS	Cancer
VIA Impression	Normal					
	Inflammation					
	Dysplasia					
	Cancer					

Figure 10

		CerviScope	
		No lesion seen	Lesion seen
VIA	No Lesion seen		
	Lesion seen		

Figure 11

		CerviScope		
		No lesion seen	Non-suspicious lesion	Suspicious lesion
VIA	No lesion seen			
	Non-suspicious lesion			
	Suspicious lesion			

Figure 12

		CerviScope Impression			
		White Epithelium	Punctation	Mosaiciam	Atypical Vessels
VIA Impression	White Epithelium				
	Punctation				
	Mosaicism				
	Atypical Vessels				

Figure 13

Feedback:

The features of the “CerviScope” that could be improved are:

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The features of the “CerviScope” that I did not like are:

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The features of the “CerviScope” that I particularly liked are:

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The features of the “CerviScope” that I would like to see added are:

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Additional comments:

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