TO: Clark Burnham, Ph.D.
Chairman, Institutional Review Board

FROM: Rebecca Richards-Kortum
Assistant Professor of Electrical and Computer Engineering

DATE: June 10, 1997

SUBJECT: Review of Protocol Entitled "Measurement of Fluorescence EEM of Cervical Intraepithelial Neoplasia"

Enclosed please find 12 copies of a protocol entitled "Measurement of Fluorescence EEM of Cervical Intraepithelial Neoplasia." This protocol describes a study to collect fluorescence excitation - emission matrices (EEMs) and diffuse reflectance measurements *in vivo*. Specifically, EEMs and diffuse reflectance will be recorded from sites in the ectocervix and outer endocervix. This study will be conducted in conjunction with the Department of Gynecologic Oncology at the U.T. M.D. Anderson Cancer Center in Houston. This study is very similar to our previous study entitled "Screening Method for Cervical Neoplasia Based on Fluorescence Spectroscopy" except that it will be conducted with an improved instrumentation and fiber-optic probe. The new instrumentation will enable us to record an entire EEM in about 2.5 minutes. This will enable us to evaluate and validate the wavelengths selected from previous *in vitro* studies, and to identify additional wavelengths that may better classify tissues as normal, inflamed, metaplasia, HPV, CIN I, CIN II, and CIN III.

This protocol has been jointly submitted to the IRB at U.T. Austin and the Surveillance Committee at the M.D. Anderson Cancer Center. We have used the protocol form required by M.D. Anderson because the patients will be seen there. Please let me know if I can provide you with any additional information regarding this protocol.

SYNOPSIS OF PROPOSAL

Title of Study:

Measurement of Fluorescence EEM of Cervical Intraepithelial Neoplasia

1. This study will be a joint study of The Biomedical Engineering Program at The University of Texas at Austin and the Department of Gynecologic Oncology at The University of Texas M. D. Anderson Cancer Center. All patient interaction will take place at M. D. Anderson. Patients for the study will consist of individuals over the age of 18 who have been referred to the U.T. M. D. Anderson Colposcopy Clinic. Patients who are pregnant are not eligible for this study.

2. Each potential subject will be asked to participate in the study by a health care provider. Formal written consent will be obtained.

3. There are no potential risks, other than the loss of confidentiality, associated with participation in the study. If they agree to participate, as part of their routine colposcopic evaluation, subjects will undergo placement of a fiber-optic probe designed to collect fluorescence spectra and diffuse reflectance from the cervix for 2.5 minutes. Measurements will be collected for excitation wavelengths from 330 to 500 nm and emission will be collected from 340 to 700 nm. The maximum intensity of tissue illumination will be 50 microwatts per square mm. There is no possibility of removal of cervical tissue due to tissue vaporization or charring. These levels are known to produce no measurable physical changes in tissue such as dehydration. The probe will be disinfected by the standard methods used for colposcopic instruments.

4. Confidentiality of patients will be preserved; patient names will not be revealed in publications or reports without consent.

5. Other than colposcopic diagnosis for cervical neoplasia, there are no benefits to individual subjects who participate in this study. However, the potential for improved methods of diagnosis of CIN may ultimately benefit all patients who have an increased risk for developing CIN.

6. Subjects entered into this study incur risks normally associated with colposcopy and colposcopically directed biopsies.. These are the same risks incurred by patients not electing to participate in the study. This project may ultimately benefit all patients at risk for CIN by providing a more accurate way of directing biopsy placement for the diagnosis of CIN.

7. All *in vivo* studies will be performed at the M. D. Anderson Cancer Center under the direction of Dr. Michele Follen Mitchell.

8. N/A

9. N/A

10. This project has been jointly submitted to the Surveillance Committee at the UT M. D. Anderson Center.

The University of Texas at Austin
Department of Electrical and Computer Engineering
Biomedical Engineering Program

Protocol Title: Measurement of Fluorescence EEM of Cervical Intraepithelial Neoplasia (CIN)

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1.0 Objectives

The overall objective of this study is to identify potential improvements for a noninvasive method of diagnosing dysplasia and neoplasia in the cervix using fluorescence and reflectance spectroscopy.

1.1 To measure the reflection and fluorescence spectra *in vivo* of sites in the human cervix.
1.2 To further refine the fluorescence spectroscopy system for detection of cervical lesions via better classification of normal columnar tissue, non-neoplastic tissue with inflammation, and low and high grade SIL.
1.3 Evaluate and validate the wavelength selections for the spectroscopy device derived from *in vitro* measurements.
1.4 Determine the sensitivity and specificity of this device for diagnosis of CIN.
1.5 Compare the device performance to colposcopy and pathologic analysis of tissue removed at colposcopy.

2.0 Background

2.1 Cervical Intraepithelial Neoplasia (CIN)

The most prevalent of preinvasive conditions of the female lower genital tract is cervical intraepithelial neoplasia (CIN). The traditional definition calls it a "spectrum of intraepithelial changes that begins as a generally well differentiated intraepithelial neoplasm, which has traditionally been classified as a very mild dysplasia, and ends with invasive carcinoma." [1] Neoplastic changes are confined to the squamous epithelium and include nuclear pleomorphism, loss of polarity, and presence of abnormal mitoses. Cervical intraepithelial neoplasia is graded 1 to 3, based on the amount of undifferentiated cells present from the basement membrane to the surface epithelium. When one third of that distance is involved , the grade is 1; when more than one third and up to two thirds is involved, the grade is 2; when more than two thirds is involved, the grade is 3. Full-thickness involvement from the surface epithelium to the basement membrane is referred to as carcinoma in situ (CIS). [1] The median transit time from CIN to CIS depends on the grade of CIN: for CIN I, the time is approximately six years; for CIN II, approximately two years; and for CIN III, approximately 1 year. [2] Despite some debate in the past about CIN and CIS representing two distinct entities, it is currently believed that CIN and CIS are part of a spectrum of disease that leads to invasive cancer of the cervix. The diagnosis and treatment of CIN are thus part of the prevention of invasive cervical cancer. The tissues studied in this protocol will be classified according to the new Bethesda system. [1] Lesions with HPV and CIN will be classified as SIL's where they will be further separated as high grade SIL (CIN II, CIN III, CIS) and low grade SIL (CIN I, HPV). Normal, metaplastic and non-specific inflammation tissues will be classified as non-SILs.

2.2 Limitations of Current Diagnostic Methodologies

Cervical intraepithelial neoplasia is usually detected by screening Pap smears from asymptomatic women. Patients with abnormal Pap smears are referred for colposcopy and possibly biopsy. Acetic acid is applied to the cervix, and areas with abnormal DNA content, such as those with CIN, turn white. The colposcope, a mounted magnifying lens is used to direct biopsies of the abnormal white areas. Abnormal configurations of blood vessels, called vascular atypia, signal disordered growth and help the clinician know which other areas require biopsy. [3] An appropriate evaluation of the abnormal Pap smear involves review of the referral and repeat Pap smears, endocervical curettage, and multiple biopsies of the aceto white areas; the results of such analysis will indicate whether the patient has CIN. [4]

Reid [5,6] et. al. feel that the predictive accuracy of colposcopy is excellent. Their colposcopic index which includes an evaluation of white epithelium and vascular atypia, as well as a Schiller Stain has a predictive accuracy of over 90% in 72 patients. Barrasso [7] et. al. disagree. In a blinded study of >200 patients, they found the predictive ability of colposcopy to be poor for CIN but good for condyloma.

2.3 Spectroscopic Diagnosis of Disease

The focus of the previous research of one of the investigators has been to develop a general method for spectroscopic diagnosis of disease which can be applied to any tissue. [8] The approach for developing spectroscopic diagnostic algorithms for disease in tissue is described here. Initially, the spectra of normal and diseased tissues are characterized *in vitro* over the entire visible wavelength space to determine regions of the spectrum most promising for further study. In these wavelength regions, the spectra of normal and diseased

tissues are studied in detail *in vitro* and *in vivo,* in order to verify the sensitivity and specificity with which this technique can be used to diagnose disease. Microscopy studies are initiated in the wavelength regions where most effective discrimination can be achieved to identify the morphologic and biochemical structures responsible for fluorescence and to measure their spectra. This information is used within a model of tissue fluorescence to extract biochemical parameters from tissue spectra, thus providing a quantitative method of data analysis. The model is then applied to the data base of spectra collected *in vitro* and *in vivo,* and these parameters are used to develop a diagnostic algorithm which can be used to classify tissue type, to determine the ultimate performance of the technique. Finally, the algorithm so determined is prospectively tested on additional data sets obtained *in vivo*. This method has been successfully applied to the development of a diagnostic algorithm for atherosclerosis, [9] for colonic dysplasia,[10][11] for urinary bladder carcinoma [11] and most recently, cervical carcinoma.[12] [13] Thus, the feasibility of this method of diagnosis has been demonstrated in several tissue systems, including three types of neoplasia.

To analyze tissue *in vivo*, a system was developed consisting of a fiber optic probe to be placed directly against the tissue to be analyzed, a nitrogen pumped dye laser and an optical multi channel analyzer. The probe delivers laser light at a specific excitation wavelength and collects fluorescence from the entire emission wavelength range from the mucosa. Presently the probe design allows evaluation of a 1mm diameter segment of mucosa.

This system was used at MD Anderson (Protocol #GYN93-008) to differentiate cervical intraepithelial neoplasia (CIN) from non-neoplastic abnormal tissue and normal cervical tissues. During colposcopy, spectra were collected from each colposcopically abnormal area of the cervix prior to biopsy and from 1 to 4 colposcopically normal areas. Data collection required only 375 ms per site. Data were obtained in 28 patients from a total of 66 colposcopically normal areas and 49 histologically abnormal areas (5 inflammation, 21 HPV changes and 23 CIN).[12] Normal cervical fluorescence spectra display a broad fluorescence peak from 400-442 nm. In addition, it was noted that the fluorescence intensity of the tissue varied by more than a factor of five from patient to patient, while variation within a patient was less than 10%. The spectra of samples showing inflammation and HPV changes peak near 442 nm. Finally, the spectra of CIN samples display a broad fluorescence peak ranging from 442 to 460 nm. A standard one sided paired t-test was employed to test two hypotheses: 1) that the average relative intensities of normal tissues were greater than those of abnormal tissues from the same patients, and 2) that the average relative intensities of tissue showing HPV changes were greater than those of tissue showing CIN in the same patient. Hypotheses #1 and #2 were found to be true below the 0.005 and 0.05 level of significance, respectively.

These differences were exploited to define a two stage algorithm for diagnosing CIN. A simple paired algorithm was first used to differentiate histologically abnormal tissues from colposcopically normal tissues from the same patient. This algorithm correctly diagnosed histological abnormality with a sensitivity, specificity, and positive predictive value of 92%, 90% and 88%. The second stage of the algorithm classified abnormal tissues as neoplastic or non-neoplastic with a sensitivity of 87%, a specificity of 73% and a positive predictive value of 74%.[12] These results suggest that *in vivo* fluorescence spectra of the cervix can be used in the recognition and differential diagnosis of CIN at colposcopy.

We are currently adapting the above system to use fluorescence to better discriminate between normal and abnormal cervical tissue *in vivo*, especially in regard to tissues with inflammation. It also will provide more effective patient management, as 1) fluorescence measurements, and hence diagnostic information, can be obtained in real time and 2) the technique is non-invasive.

Our newly developed system will allow us to collect an entire excitation - emission matrix (EEM) *in vivo*. An EEM is the fluorescence emission matrix as a function of both excitation and emission wavelength. Previously this measurement was prohibitively time consuming, but this system is capable of obtaining an entire EEM in about 2.5 minutes. This is significant because the entire matrix of information can be collected in a realistic clinical time frame. The entire data matrix is necessary for complete research analysis of the relevant spectral data. Once the spectral location of the diagnostically relevant data is known, only information at those spectra need be collected. Thus, subsequent diagnostic systems will not require the collection of the entire EEM, and information collection time will be further reduced.

The system that will be used in this study has several modifications. In order to accomplish multiple excitation wavelengths, a mercury lamp and scanning monochrometer will take the place of the laser in previous systems. The excitation light is coupled into the fiber optic probe. Fluorescence emission as well as reflectance signals are collected by the probe and coupled into a scanning imaging spectrograph fitted with a high sensitivity CCD array. The CCD fitted spectrograph is capable of reading multiple emission intensities simultaneously, facilitating the much shorter EEM collection time of this instrument compared to previous scanning instruments. The collection efficiency of the system has been optimized and instrumentation components were selected specifically for this application. Measurements will be collected for excitation wavelengths from 330 to 500 nm and emission will be collected from 340 to 700 nm. The maximum intensity of tissue illumination is 50 microwatts per square mm, below that which would induce any thermal or optical change. A single EEM measurement will take approximately 2.5 minutes.

3.0 BACKGROUND TREATMENT INFORMATION

Colposcopically directed biopsies are routinely used in the diagnosis of CIN. This preinvasive condition is routinely diagnosed through an abnormal Pap smear. These patients are referred for colposcopy and multiple samples of abnormal tissue are taken.

4.0 ELIGIBILITY

Patients over the age of 18, who have been referred to the U.T. M.D. Anderson Colposcopy Clinic are eligible for this study. Patients will be considered ineligible if they are pregnant. Patients must sign an informed consent indicating awareness of the investigational nature of this study.

5.0 TREATMENT PLAN

As part of their routine colposcopic evaluation, patients will undergo placement of the probe on three sites in the cervix for 2.5 minutes. Two colposcopically abnormal sites and one normal site, alternating between columnar tissue and squamous tissue, will be measured. If only a single colposcopically abnormal sites is present, the abnormal site, one columnar, and one squamous site will be measured. For patients undergoing colposcopy, only the colposcopically abnormal areas will be biopsied. For patients undergoing therapy with the loop electro-surgical excision procedure (LEEP), one additional biopsy will be taken from a colposcopically normal site.

6.0 PRETREATMENT EVALUATION

All patients referred to U.T. M.D. Anderson Colposcopy Clinic undergo history, physical exam, Pap smear, wet drop gonorrhea cultures, and colposcopically directed biopsies of the cervix and endocervix. Outside Pap smears are sent in for review and discrepancies are resolved.

7.0 EVALUATION DURING STUDY

This study requires a one time measurement of the cervix which takes 2.5 minutes per site. Three sites will be measured for each patient. Patients will be subjected to routine care which involves treatment for cervical intraepithelial neoplasia, if present, and follow-up at four month intervals.

8.0 CRITERIA FOR RESPONSE

Not applicable

9.0 CRITERIA FOR REMOVAL FROM THE STUDY

Not applicable

10.0 STATISTICAL CONSIDERATIONS

The purpose of this study is to determine the extent to which algorithm performance can be improved by the incorporation of addtional wavelengths. We wish to better discriminate squamous normal (SN), columnar normal (CN), inflammation, low grade SIL (LG), and high grade SIL (HG). We will measure algorithm performance using the metrics of sensitivity and specificity. Our previous research [paper in progress] has shown that a sample size of 100 patients is required to estimate sensitivity and specificity within 5% of true values. Briefly, this estimate is based upon the convergence of a family of receiver operator characteristic (ROC) curves as the sample size is increased. At the conclusion of this study, we will examine the results and submit a second protocol to acquire additional data if required.

11.0 DATA AND PROTOCOL MANAGEMENT

The principal investigator will be responsible for the management of the protocol. The data will be collected at U.T. M.D. Anderson Colposcopy Clinic and analyzed at the Spectroscopy Laboratory at the University of Texas at Austin.

12.0 REPORTING REQUIREMENTS

Any adverse effects of this protocol will be reported to the Surveillance Committee.

13.0 REFERENCES

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The University of Texas
M.D. Anderson Cancer Center

INFORMED CONSENT

PROTOCOL TITLE: Measurement of Fluorescence EEM of Cervical Intraepithelial Neoplasia

1. _____ _____
Participant's Name ID Number

You have the right to know about the procedures that are to be used in your participation in the clinical research so as to afford you an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm you; it is simply an effort to make you better informed so may give or withhold your consent to participate in clinical research. This informed consent does not supersede other informed consents you may have signed.

This clinical trial is so designed that no person shall on the grounds of race, color, gender, or national origin be excluded from participation in or be denied the benefits, or be otherwise subjected to discrimination through or under this study.

DESCRIPTION OF RESEARCH:

2. PURPOSE OF THE STUDY: This clinical research study is designed to help the investigator develop a new technique using tissue fluorescence to diagnose premalignant and malignant lesions in the cervix.

3. DESCRIPTION OF RESEARCH: Laboratory studies have demonstrated that laser induced fluorescence spectroscopy can distinguish between precancerous and normal tissues. This work may provide a new way of detecting pre-cancer with greater accuracy at an earlier stage. The use of laser induced fluorescence spectroscopy to differentiate tissue is regarded as research and is being undertaken to develop techniques for the application of tissue spectroscopy in humans and to use these techniques in the diagnosis of cervical lesions. Fluorescence spectroscopy involves a one-time reading of the chemical make-up of tissues in the cervix. Readings take about 2.5 minutes. A disinfected probe will be inserted into the cervix. The probe is attached to a machine that measures the wavelengths produced by the molecules present in the cells of the cervix. The device has been approved only for experimental medical use. This study will include 100 women here at M. D. Anderson Cancer Center. If the individual participates, small amounts of laser light will be directed at several (1-3) selected areas of the cervix. Those patients undergoing loop electro-surgical excision procedures (LEEP) will have one additional biopsy taken from a colposcopically normal site.

Before the procedure, patients will have a pregnancy test to ensure the participants are not pregnant, and a Pap smear. Patients will be asked about their medical history.

4. RISKS, SIDE EFFECTS, and DISCOMFORTS TO PARTICIPANTS: Patients may feel slight discomfort when the probe is inserted into the cervix. Cervical tissue will not be removed, burned, dried out, or harmed by the probe. The risks of colposcopy will be covered in another consent form.

5. POTENTIAL BENEFITS: There will not be any immediate or direct benefit to the participants who take part in this study. Fluorescence spectroscopy may someday be helpful for confirming whether patients have cervical intraepithelial neoplasia.

6. ALTERNATIVE PROCEDURE OR TREATMENTS: Patients who take part in this study must have findings from pap smears that show the presence of abnormal cells. Colposcopy is recommended for these patients. Patients do not have to take part in this study to receive colposcopy.

UNDERSTANDING OF PARTICIPANTS:

7. I have been given an opportunity to ask any question concerning the procedures involved and the investigators have been willing to reply to my inquiries. This procedure will be done under the above numbered, titled and described clinical research protocol at this institution. I hereby authorize, _____, the attending physician/investigator and designated associates to perform the procedure.

8. I have been told and understand that my participation is voluntary, that I am able to withdraw my consent and to discontinue my participation in this study at any time. Such action will be without prejudice and there shall be no penalty or loss of benefits to which I may otherwise be entitled, and I will continue to receive treatment by my physician at this institution. Should I decide not to participate or withdraw my participation from this clinical research, I have been advised that I may discuss any consequences or effects of my decision with my physician.

In addition, I understand that the investigator may discontinue the clinical research study, if, in the sole opinion and discretion of the investigator, the study or treatment offers me little or no future benefit, or other causes prevent continuation of the clinical research study. The investigator will notify me should such circumstances exist and my physician will advise me about available treatments which may be of benefit at that time.

I will be informed of any new findings developed during the course of this clinical research study which may relate to my willingness to continue participation in the study.

9. I have been assured that confidentiality will be preserved except that qualified monitor from the Food and Drug Administration (FDA) may review my records where appropriate and necessary. Qualified monitors shall include assignees authorized by the Surveillance Committee of this institution provided that confidentiality is assured and preserved. My name will not be revealed in any reports or publications resulting from this study without my expressed consent. In a special circumstance, the FDA might be required to reveal the names of the participants.

10. I have been informed that should I suffer any injury as a result of participation in this research activity, reasonable medical facilities are available for treatment at this institution. I understand however that I cannot expect to receive any credit or reimbursement from this institution or any financial compensation from this institution for such injury.

11. I have been informed that I should inquire of the attending physician whether or not there are any services, investigational agents or devices, and/or medications being offered by the sponsor of this clinical research project at a reduced cost or without cost. Should the investigational agent become commercially available during the course of the study, I understand that I may be required to cover the cost of subsequent examinations.

Costs related to my medical care including expensive drugs, tests or procedures that may be specifically required by this clinical research study shall be my responsibility unless the sponsor or other agencies contribute toward said costs. I have been given the opportunity to discuss the expenses and costs associated with my participation in this research activity.

12. It is possible that this research project will result in the development of beneficial treatments, new drugs, or possible patentable procedures, in which event I herein disclaim and hereby waive any right to claim to receive

any compensation or benefits from the subsequent use of information acquired and developed through participation in this research project.

13. I understand that refraining from breast feeding and practicing effective contraception is medically necessary and a prerequisite for my participation in this clinical research study. Should contraception be interrupted or if there is any suspicion of pregnancy, my participation in the clinical research study will be terminated at the sole discretion of the investigator.

14. I may discuss questions or problems during or after this study with Dr. Michele Follen Mitchell at (713) 792-7462. In addition, I may discuss any problems that I may have or any questions regarding my rights during or after this study with the Chairman of the Surveillance Committee at (713) 792-3220 and may in the event any problem arises during this clinical research contact the parties named above.

CONSENT

Based on the above, I consent to participate in the research, and have received a copy of the consent form.

Date	Signature of the Participant
Witness Other than Physician or Investigator	Signature of Person Responsible and Relationship

I have discussed this clinical research study with the participant and/or his or her authorized representative, using a language which is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks, and I believe the participant understood this explanation.

Physician/Investigator

I have translated the above informed consent into _____ for this patient.
Name of the language

Name of translator	Signature of Translator and Date