TITLE PAGE

TITLE: Acetic acid chromoendoscopy in Barrett's esophagus surveillance is superior to the standardized random biopsy protocol in detecting neoplasia: A prospective randomized trial.

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CTRC/CTMS# 16-0087
IND#: 129137PROTOCOL V 1.3
DATE: 17 Nov 2016

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Protocol UTHSCSA CTMS# 16-0087 and will adhere to the study requirements as presented, including all statements regarding confidentially. In addition, I will conduct the study in accordance with current international conference on harmonization (ICH) guidance, Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations and local IRB and legal requirements.

Name of Clinical Investigator: **Ingrid Chacon, MD**

Institution: **Doctors Hospital at Renaissance**

_____ _____

Investigator Signature Date

ABBREVIATIONS (sample list – please only use those that are relevant to your protocol)

AA	Acetic Acid
AE	Adverse Event
DHR	Doctor's Hospital at Renaissance
DSM	Data Safety Monitoring
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety and Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IIS	Investigator Initiated Protocol
IND	Investigational New Drug
IRB	Institutional Review Board
NIH	National Institutes of Health
ORA	Office of Research Administration
PI	Principal Investigator
PRC	Protocol Review Committee
PRF	Protocol Review Form
PRMS	Protocol Review and Monitoring System
SAE	Serious Adverse Event
UTHSCSA	University of Texas Health Science Center at San Antonio
SBP	Standardized random Biopsy Protocol
AAC	Acetic Acid Chromoendoscopy
ICF	Informed Consent Form
BP	Blood Pressure
HR	Heart Rate
BMI	Body mass index
BX	Biopsy
SOC	Standard of Care

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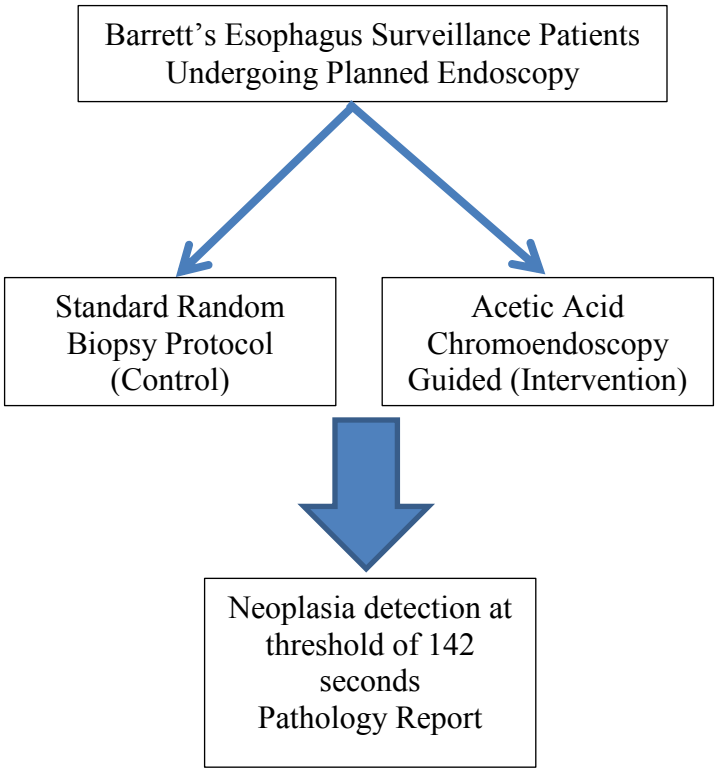
PROTOCOL SYNOPSIS

PROTOCOL TITLE: Acetic acid chromoendoscopy in Barrett's esophagus surveillance is superior to the standardized random biopsy protocol in detecting neoplasia: A prospective randomized trial.
STUDY PHASE: 3
INDICATION: Barrett's esophagus undergoing chromoendoscopy surveillance for neoplasia.
PRIMARY OBJECTIVE: To compare the neoplasia yield when using acetic acid chromoendoscopy versus the neoplasia yield from standardized random biopsy protocol in Barrett's esophagus surveillance population at Doctor's Hospital at Renaissance.
SECONDARY OBJECTIVE: N/A
HYPOTHESIS: Acetic acid chromoendoscopy will be able to detect more neoplasias in comparison to standard, random biopsies in Barrett's esophagus surveillance population.
STUDY DESIGN: Prospective randomized study
PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS: Percent (%) neoplasia detection in 2 groups: Random Biopsy Protocol (control) and Acetic Acid Chromoendoscopy (treatment group)
SAMPLE SIZE BY TREATMENT GROUP: 104 patients randomized into two groups with 1:1 ratio.
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA: Patients 18 years and older with a previous diagnosis of Barrett's esophagus, confirmed by pathology.
INVESTIGATIONAL PRODUCT DOSAGE AND ADMINISTRATION: 10cc of 2.5% Acetic Acid
CONTROL GROUP: Standard Random Biopsies
PROCEDURES: Acetic Acid Chromoendoscopy Guided Biopsies

SCHEMA



1. OBJECTIVES

1.1 Primary Objective

The objective of this study is to compare the neoplasia yield when using acetic acid chromoendoscopy versus the neoplasia yield from standardized random biopsy protocol in our Barrett's esophagus surveillance population.

2. BACKGROUND

2.1 Study Disease

Barrett's esophagus is the single most important precursor lesion and risk factor for esophageal adenocarcinoma. It develops when the squamous esophageal epithelium is replaced by columnar epithelium (resulting in intestinal metaplasia) during the process of healing after repetitive injury, and is typically associated with gastro esophageal reflux disease. Intestinal metaplasia can be detected in most patients with esophageal adenocarcinoma. Patients diagnosed with Barrett's esophagus are followed at established intervals with surveillance endoscopy. These intervals are based on American College of Gastroenterology Clinical Guidelines for the diagnosis and management of Barrett's esophagus. Endoscopic examination of the esophageal mucosa and random biopsies may help to find neoplasia at an early stage. Patient's found to have earlier neoplasia have the best prognosis (Shaheen, Falk, & Iyer, 2016).

2.2 Investigational Agent or Device

Acetic acid is a commonly available dye that has been used in the detection of neoplasia of the uterine cervix and in Barrett's esophagus. Several studies have been performed using acetic acid as a chromoendoscopy agent to increase the yield of biopsies on Barrett's esophagus surveillance. Few studies, mostly retrospective cohort studies, utilizing this detection modality have been reported in literature. (Curvers, W Gastroenterology 2010) (Pohl J Endoscopy 2007)

2.3 Rationale

Neoplasia in Barrett's esophagus is often focal and can be missed by no targeted biopsies alone. Meta-analysis of 24 studies involving patients with Barrett's esophagus revealed a 25% missing rate of esophageal neoplasia after index endoscopy (Visrodia, Singh 2016).

Despite of current knowledge and recommendations by national societies, the adherence of biopsy protocol guidelines in the US community setting is not ideal. A review of 2245 Barrett's esophagus cases showed 51.2% adherence to guidelines. Non-adherence to guidelines is associated to decreased neoplasia detection (Abrams, Kapel, & Linberg, 2009). In recent years, various advanced endoscopic techniques have been utilized, but with varying success rates. Narrow-band imaging, trimodal imaging, spectral imaging, confocal laser endomicroscopy and i-scan are technologies that are manufacturer dependent with limited varying success rates and have financial implications (Pohl J, May 2007) (Curvers, Wallace 2010) (Gupta A, Attar 2014). Narrow band imaging is routinely utilized as a diagnostic tool for

detecting Barrett's esophagus at Doctors Hospital at Renaissance. Acetic acid is a commonly available dye that has been used in the detection of neoplasia in Barrett's esophagus. Few studies, mostly retrospective cohort studies, utilizing this detection modality have been reported in literature. A large retrospective cohort study compared neoplasia detection rate in 627 patients with Barrett's esophagus undergoing surveillance. Patients had spray of esophageal mucosa with acetic acid before biopsies. Targeted biopsies were taken at areas with lack of acetowhitening or abnormal surface patterns. Pathology results were compared retrospectively with surveillance patients who had standard biopsies in the past. In the acetic acid cohort there was a 14.7 fold increase in neoplasia detection compared with the standard random biopsy protocol group. (Shareef Tholoor… Bhandari, Gastrointestinal endoscopy). A prospective cohort study of 132 patients with Barrett's esophagus reported also increased sensitivity for neoplasia after acetic acid spray. Patients were given acetic acid spray before esophageal biopsies. Targeted biopsies of any neoplasia and quadrantic 2-cm biopsies of residual Barrett's area were then taken. Using a threshold of 142 seconds after spray yielded a sensitivity for neoplasia of 98 % (95 % confidence interval [95 %CI] 89 % - 100 %) and specificity of 84 % (74 % - 91 %) (Bhandari 2013). Current guidelines don't recommend the use of these modalities in lieu of random biopsy protocol. (Shaheen, Falk & Lyer 2016)

Recent meta-analysis of 24 cohort studies concluded that among patients with non dysplastic Barrett's esophagus (or BE with low grade dysplasia) at their index endoscopy, 25% of esophageal adenocarcinoma was diagnosed within a year. These cases are considered missed esophageal carcinoma by definition. A more sensitive technique for Barrett's esophagus surveillance should be allocated to decrease the incidence of missed esophageal adenocarcinoma.

3. PATIENT SELECTION

3.1 Inclusion Criteria

- Patients 18 years and older
- Previous diagnosis of Barrett's esophagus, confirmed by pathology.

3.2 Exclusion Criteria

- Patients diagnosed with any level of dysplasia on previous esophageal biopsies.
- Patients who had esophageal therapy with Halo radiofrequency ablation in the past, or esophagectomy.
- History of allergy to Acetic Acid
- History of esophageal dysplasia or cancer
- Esophageal ulcerations
- Esophageal Candida
- Esophageal Varices
- Patients who cannot provide a valid consent
- Patients who are currently pregnant

4. PROCEDURES

4.1 General Guidelines

All DHR employed gastroenterologists will participate in the study. All procedures will be performed by trained and experienced Endoscopists. DHR Research Institute will ensure that all participating Gastroenterologists and pathologists are instructed on consenting, source documentation requirements, Good Clinical Practice (GCP) guidelines and additional study related topics. Dr. Chacon, the Study Principal Investigator will be responsible for training Gastroenterologists and Endoscopists on the technique. She will ensure that all Gastroenterologists and Endoscopists are qualified to perform the technique in a standardized fashion. All key study personnel will sign a training affidavit attesting to their knowledge of study processes.

Eligible subjects will be randomly allocated to either the intervention arm of acetic acid chromoendoscopy or the non-intervention arm of standardized random biopsy protocol. Source documentation verifying eligibility, along with the eligibility checklist and consent will be verified by Dr. Chacon and kept in subject's chart.

4.2 Informed Consent Process

Study candidates will be identified through DHR's Barrett's surveillance program. Research staff and Gastroenterologists who are permitted to consent patients will describe the trial in detail. All patients will be made aware that they are under no obligation to participate, that failure to participate will not adversely affect their care, and that they may decline participation at any time. They will be given an opportunity to ask questions and have these answered to their satisfaction. The informed consent will then be signed and dated by both the patient and the principal Investigator. In general, patients who are deemed competent to sign an informed consent for their procedure will be deemed competent to evaluate whether or not they wish to participate in this trial. If there are any questions regarding competence, the trial will not be offered to the patient. Patients who have agreed to participate and have signed the informed consent will participate.

4.3 Randomization Procedures

Prior to the initiation of the study, the DHR Research Institute will create a randomization list. Patients will be randomized to one of the two treatment arms and assigned randomization # with a 1:1 allocation ratio. Prior procedure, the delegated research associate will assign the patient to a treatment arm and the Gastroenterologist will then be instructed to perform procedure according to the randomization group.

5. RESEARCH PLAN

5.1 Research Plan Administration

Study candidates will be identified through DHR's Barrett's surveillance program. Patients who have agreed to participate and have signed informed consent will participate. Patient's eligibility information will be verified by the Principal Investigator. The patient will then be randomized prior to their scheduled endoscopy. For the control group, the

Gastroenterologist will follow routine procedure. For the intervention group, acetic acid chromoendoscopy will be performed. All Gastroenterologists participating in the study will be educated on the application and documentation of this procedure. Patients will receive routine follow up care as per DHR policy.

Pre-Procedure:
Gastroenterologists will provide the following information to Dr. Chacon to verify eligibility.

1. History and physical notes
2. Eligibility checklist
3. Informed consent form

Delegated Research Associate will assign a number and allocation to the gastroenterologist.

Procedure:

Control group: Random biopsy protocol

- Patients assigned to no intervention arm will have a random biopsy consisting of 4 quadrant biopsies every 2 cm of Barrett's esophagus (from proximal to distal).
- If abnormality is seen such as mucosal ulceration, mucosal nodularity, abnormal vessels, additional biopsy will be taken and identified as targeted.

Samples collected will be labeled as random or targeted.

Intervention group: Acetic Acid protocol

Acetic Acid will be pre-prepared by DHR Pharmacy

Patients assigned to AA arm will be given spray of the mucosa with 10 cc of 2.5% of AA via scope. Physician will allow 142 seconds for the acetowhitening effect to happen.

- If no abnormal mucosa seen, physicians will biopsy the mucosa according to the random biopsy protocol; meaning the physician will take 4 quadrant samples every 2 cm of Barrett's Esophagus (from proximal to distal).
- If abnormality is seen (lack of acetowhitening effect) physician will take biopsies on target (abnormal mucosa) plus random biopsy as per protocol. Targeted biopsies will be labeled as such.

Biopsies will be labeled and sent to pathology as per Doctors Hospital at Renaissance protocol. Samples will be identified with patients name, medical records number, and research identification number. Pathologist will be blind to patient's participation arm.

Patient is given information in writing and contact numbers in case s/he experiences symptoms.

Post-Procedure, Pathology:

All specimens will be sent to pathology. These specimens will be reviewed by a pathologist who will be blinded to patient's participation arm. Any discordant results will be reviewed by an outside expert pathologist.

All biopsies will be obtained in appropriate biopsy containers, properly labeled and submitted to pathology department. Biopsies are fixed for a minimum fixation time of 6

hours. They are properly identified and transferred to appropriate cassettes. In order to identify these cases, cassettes will be color coded. The cassettes are placed in a tissue processor wherein the steps performed include fixation, dehydration, clearing and wax infiltration. After this process, tissue cassettes are removed embedded with proper orientation. 3-5 micron thick serial sections (6) are obtained with a sharp clean knife and transferred on to a glass slide. These slides are stained, utilizing Hematoxylin and Eosin automated stained and cover slipped.

Two pathologists independently review the slides, and record their diagnosis. If there is discordance, slides will be sent to independent outside pathologist with gastrointestinal expertise for review. Final results will be recorded on an excel document and will be made available for statistical analysis.

Gastroenterologists will provide the following to Dr. Chacon:

1. Copy of the procedure note
2. Copy of the pathology report which includes the following
    a. Data regarding specimen and
    b. Other clinicopathologic data.

5.2 General Concomitant Medication and Supportive Care Guidelines

All of the procedures described in this study are standard of care (SOC). There is no additional substantive risk associated with Acetic Acid.

5.3 Duration of Therapy

Treatment is limited to the surgical intervention. Routine adjuvant care will be given.

5.4 Duration of Follow Up

N/A. No follow up period.

5.5 Criteria for Removal from Study

Patients will remain in the study unless there is an intraprocedure catastrophe that mandates an incomplete procedure; or if they choose to withdraw.

5.6 Alternatives

Chromoendoscopy is a commonly accepted procedure and there is no increased risk with the addition of acetic acid to this procedure. All precautions will be taken to minimize overall procedural risk. Alternatives to the study would be to have standard of care in which patients will be informed of.

5.7 Compensation

Patients will not be paid for participating in this study.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

6.1 Procedure Related

Expected adverse effects for this study include an allergic reaction to the acetic acid.

6.2 Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are listed below.

Adverse Event (AE) Any untoward or unfavorable occurrence in a human research subject (physical or psychological harm) temporally associated with the individual's participation in the research (whether or not considered related to participation in the research).

Related: There is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research. The term AE is used to include both serious and non-serious AEs.

Serious adverse event: A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, and washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above?

6.3 Recording and Reporting of Adverse Events

Non-serious adverse events and SAEs will be collected throughout the study period. Only Serious unexpected adverse events will be collected and reported to the Institutional Review Board. Adverse events should be reported to the IRB within 5 days of discovery of the adverse event.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to other medication

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Definitions. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

6.4 Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnosis is preferred to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.5 Causality collection

The causality of SAEs (their relationship to study procedures) will be assessed by the PI and reported to the IRB.

6.6 Adverse Events Characteristics

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

Attribution of the AE:

Definite – The AE *is clearly related* to the study treatment
Probable – The AE *is likely related* to the study treatment
Possible- The AE could be related to the study treatment
Unlikely – The AE *is doubtfully related* to the study treatment
Unrelated – The AE *is clearly NOT related* to the study treatment

7. INVESTIGATOR RESOURCES

7.1 Qualifications

Multiple Gastroenterologists at Doctors Hospital at Renaissance and the DHR Research Institute will conduct this study. All study personnel will be required to complete the requisite Human Subjects Protection Training by CITI. Documentation of training will be kept on file.

Once this study has completed all regulatory requirements including the following; IRB approval of protocol, completion of all required Human Subjects Protection Training (HSPT), CV's and Medical Licenses for participating gastroenterologists, Confidential Disclosure

Agreements (CDA) and other regulatory documents as required, there will be a protocol training meeting to ensure that all Gastroenterologists, pathologists and study staff are trained in the protocol, procedures, and their responsibilities. Should there be any questions that arise during the study, all investigators and research staff will be provided with the PI's, and PM's contact information and encouraged to contact them with any questions.

7.2 Use of Facilities

All study procedures will be performed at Day Surgery at Doctors Hospital at Renaissance according to local policy and procedures.

8. STUDY CALENDAR

	Pre-Study Visit	Procedure day
Informed Consent	X	
Demographic Data	X	
Medical History	**X**	
Concomitant Medication Review	**X**	
Physical Exam	**X**	
Weight (lbs.)	**X**	
Height (in)	**X**	
BMI	**X**	
Inclusion/Exclusion Criteria	**X**	
Randomization	**X**	
Chromoendoscopy or SOC Bx		**X**
Collection of AE's*		**X**
Procedure Report		**X**
Pathology Report		**X**

*Adverse Event information related to the biopsy will be collected at the time of procedure and during routine follow-up with the subject.

9. DATA/REGULATORY CONSIDERATIONS & PROJECT MANAGEMENT

9.1 Data Management

Data (source documentation) will be collected at the site and stored at DHR Research Institute in a locked, limited access room. De identified data will then be downloaded in either Excel or SPSS format for statistical analysis, which will be done on a HIPAA compatible, password protected encrypted computer at DHR Research Institute. A separate file that contains the code to link patients Study IDs to their identifiable information will be kept in a locked, limited access room at DHR Research Institute. All data entry will be performed by the study Project Manager.

9.2 Study Monitoring

The DHR Research Institute will support the PI with site management aspects of this trial. This includes but is not limited to study start-up, regulatory assistance (IRB submissions, amendments, and renewals), provision of template study forms (tracking and eligibility checklists, etc.), training, and overall project management. The DHR Research Institute will be available to provide tools to assist the study team in conducting the trial appropriately and according to GCP Standards.

Monitoring will be performed by DHR Research Institute by conducting routine monitoring visits throughout the life of the protocol. Following each routine monitoring visit, a visit report will be generated containing information on site activities, and a summary of pertinent points and action items together with a copy of the follow-up letter will be available in investigator site file.

During these monitoring visits, some of the items that will be reviewed are:
- Training of the study staff
- Site personnel qualifications to participate in the trial
- That study related documents are current
- That regulatory compliance is accomplished
- That each subject has signed the informed consent
- That the current and approved protocol is complied with (including reporting and logging of all protocol deviations)
- That all SAEs and AEs have been reported to the local regulatory and Ethics/IRB Committees, as appropriate
- That source documentation matches data entry.

9.3 Data Safety Monitoring Committee

Data and Safety Monitoring Oversight
A Data and Safety Monitoring Plan (DSMP) is required for all protocols conducted at CTRC. All protocols conducted at CTRC are covered under the auspices of the CTRC Institutional Data Safety Monitoring Plan.

The CTRC Institutional DSMP global policies provide individual trials with:
- institutional policies and procedures for institutional data safety and monitoring,
- an institutional guide to follow,
- monitoring of protocol accrual by the CTRC Protocol Review Committee,
- review of study forms and orders by the Forms Committee,
- tools for monitoring safety events,
- monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- determining level of risk (Priority of Audit Level Score – PALS) ,
- oversight by the Data Safety Monitoring Committee (DSMC), and
- Verification of protocol adherence via annual audit for all Investigator Initiated Studies by the CTRC Quality Assurance Division.

Monitoring Safety:
Due to the low risk associated with participation in this protocol, the Principal Investigator will perform primary assessment of adverse events, adverse event trends and treatment effects on

this study. The PI will conduct independent quarterly review and report findings to the CTRC Data Safety Monitoring Committee (DSMC) and the UTHSCSA IRB.

Baseline events and adverse events will be captured using the CTRC Master Adverse Events Document for each patient using CTCAE V4.03 for the grading and attribution of adverse events. Usage of the CTRC Master Adverse Events Document centrally documents:

- the event and grades the seriousness of it,
- if the event was a change from baseline,
- determines the relationship between the event and study intervention,
- if the event was part of the normal disease process, and
- What actions were taken as a result of the event?

Safety Definitions:
For this study, the following safety definitions will be applicable:

Adverse Event Definition: An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research For this study, all adverse events will be documented starting with the beginning of the endoscopy and ending with the routine follow up patients have after their procedure.

Serious Adverse Event Definition: is any adverse event that:

1. Results in death;
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity;
5. Results in a congenital anomaly/birth defect; or
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unanticipated Problems Involving Risks to Subjects or Others Definition: Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

A. unexpected (in terms of nature, severity, or frequency) given
(a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
(b) The characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance);

B. definitely related or probably related to participation in the research; and

C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Reporting Requirements

For this study, all Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on an annual basis to determine if a serious safety problem has emerged that result in a change or early termination of a protocol such as:

- dose modification,
- suspending enrollment due to safety or efficacy, or
- termination of the study due to a significant change in risks or benefits.

As per the CTRC DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance (DQA) who will promptly notify the UTHSCSA IRB.

The PI will review the Master Adverse Events documents to determine the significance of the reported events and will file the Investigator Initiated Study Annual DSMB Report Form on an annual basis with the CTRC DSMB. The Investigator Initiated Study DSMC Report Form includes information on adverse events, current dose levels, and number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality), dose adjustments with observed response, and any interim findings. Any trend consisting of three or more of the same event will be reported to the CTRC DSMB for independent review outside of the reporting cycle, which begins three months following protocol start up. Conflict of interest is avoided by the independent review of the CTRC DSMB and by ongoing independent review of adverse events trends reported to the Director of Quality Assurance.

All SAE and UPRISO's will be reported following CTRC and UTHSCSA institutional guidelines.

UTHSCSA SAE/UPRISO REPORTING REQUIREMENTS		
Type Event	Report to	Timeframe
All AE, SAE and UPIRSO	Regulatory Affairs and DQA	Same as other notification timeframes except for SAE/AE which should be reported on Monday for the prior week
SAE	CTRC DQA	within 24 hours
AE/SAE	UTHSCSA IRB	Annually
UPIRSO - all	CTRC DQA	within 24 hours of the PI determining a UPIRSO exists
UPIRSO - life threatening	UTHSCSA IRB	within 48 hours of the PI determining a UPIRSO exists
UPIRSO - non-life threatening	UTHSCSA IRB	within 7 days of the PI determining a UPIRSO exists

AE's and SAE events that occur during clinical trials with or without an Investigational New Drug (IND) application are mandatory reports submitted to FDA via Medwatch FDA F3500A *within 15 days for events that have at least a possible relationship with the drug.*

Assuring Compliance with Protocol and Data Accuracy

As with all studies conducted at CTRC, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. Source verification of data will be performed every six weeks by DHR Research Institute. Protocol compliance, data accuracy and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team, and will be reviewed by the CTRC DSMC.

10. STATISTICAL CONSIDERATIONS

Sample Size and Power

This will be a randomized balanced two-arm clinical trial of the effect of acetic acid relative to random biopsy. The primary end point will be the proportion (p) of patients with detectable neoplasia, denoted as p_{ic} in the random biopsy control arm and P_A in the acetic acid arm. Based on historical data, it is assumed that p_{ic}=0.04. It is further assumed that P_A=0.24. Based on these assumptions, two-sided testing of the null hypothesis H_o: $P_A=p_{ic}$ with Fishers Exact test and alpha=0.05, this study will attain 80% power for testing H_o with n=52 subjects per arm. Assuming no losses, a total of 104 patients will be required. [PASS Version 11, NCSS Kaysville UT 2011].

Statistical Methods

Patients will be randomized to acetic acid or random biopsy in permuted blocks of size 2. Continuously distributed outcomes will be summarized with the sample size, mean, standard deviation, median, minimum and maximum and binary and categorical outcomes will be summarized with frequencies and percentages. The number screened, the number of screen failures by reason, the number randomized, lost to follow-up by reason and treatment arm, and the number completing the study by treatment arm will be tabulated. The significance of variation the proportion of patients with detectable neoplasia will be assessed with Fishers Exact test. Treatment arms will be contrasted with regard to mean age, BMI, gender, ethnicity, and medical history. The significance of variation in treatment group with regard to mean age and BMI will be assessed with T tests or Wilcoxon tests as appropriate and variation in gender, ethnicity and medical history will be assessed with Fishers Exact tests. Adverse events, if any, will be tabulated by treatment arm. The significance of variation the occurrence of adverse events with treatment arm will be assessed with Fishers Exact tests. All statistical testing will be two-sided with a significance level of 5%. R or SAS Version 9.4 for Windows [SAS Institute, Cary, North Carolina] will be used.

Section 2: Clinical Investigator Tools for Recruitment of Minorities

Tool included in study	LIST OF TOOLS AND ACTIONS FOR INCREASING MINORITY ACCRUAL TO CLINICAL TRIALS ***For assistance with submitting IRB documents, developing materials in English and Spanish, and scheduling public service announcements, please contact MAtools@uthscsa.edu***
Yes ☐ No ☒	1. Include Clinical Trial information on CTRC website in both English and Spanish *(Please notify MAtools@uthscsa.edu).*
Yes ☐ No ☒	2. Use of Bilingual Research Team Member or Translation services
Yes ☐ No ☒	3. Identification of bilingual Patient Navigator representative of the Target Population Please Specify:
Yes ☒ No ☐	4. Informed Consent available in Spanish
Yes ☐ No ☒	6. Information Brochures in English and Spanish** *(IRB approval required)*
Yes ☐ No ☒	7. Flyers in English and Spanish (two sided, printed in English on one side and Spanish on the other).** *(IRB approval required)*
Yes ☐ No ☒	8. Public Service Announcements (PSAs) or Advertisements- Spanish Radio** *(IRB approval required)*
Yes ☐ No ☒	9. PSA's or Advertisements -Spanish newspapers (e.g., La Prensa)** *(IRB approval required)*
Yes ☐ No ☒	10. PSA's or Advertisements -Spanish Television (e.g., Univision)** *(IRB approval required)*
Yes ☐ No ☒	11. Patient Friendly Fast Facts in English and Spanish ** *(IRB approval required)*
Yes ☐ No ☒	12. Outreach to advocacy or community organizations (including presentations or awareness campaigns). Please specify:
Yes ☐ No ☒	13. Other. Please Specify:

** - It is recommended to submit any patient materials to the IRB as an amendment after the initial IRB approval has been granted

REFERENCES

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APPENDICES

Appendix A: English Informed Consent Form + HIPAA
Appendix B: Spanish Informed Consent Form + HIPAA
Appendix C: Adverse Event Log
Appendix D: Concomitant Medication Log
Appendix E: Medical and Surgical History Log
Appendix F: Patient Demographic Form