LCCC1929: Development of Patient Reported Outcomes-informed Symptom Management System (PRISMS; Feasibility)

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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PI Signature: _____

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

In this proof-of-concept study, our multidisciplinary team will conduct a pilot randomized clinical trial to test the feasibility of the innovative ***P****atient-****R****eported Outcomes-****I****nformed* ***S****ymptom Management* ***S****ystem* (PRISMS) to enhance personalized supportive care for cancer patients and caregivers during post-treatment care transition. PRISMS was formerly known as PROCESS (Patient-Reported Outcome-Informed Caregiving Education and System Management System). We will randomly assign 20 colorectal and bladder cancer (CBC) patients who transition from post-ostomy creation hospital care to self-management at home and their caregivers to either the PRISMS or usual care groups (a total of 40 individuals). We will conduct pre- and post-assessments of QOL and PRO (symptoms) at baseline upon enrollment and 3 months later. If results indicate that PRISMS is feasible and beneficial, we will design and conduct a definitive trial to examine the efficacy of PRISMS, a potentially scalable intervention that can be disseminated through oncology clinics nationwide to enhance post-treatment care for CBC patients with ostomies and their caregivers.

1.2 Background

The third and fourth most common cancers in the US respectively,[1] colorectal and bladder cancer (CBC) affects more than 100,000 patients each year.[2] CBC disproportionately affects older patients, with median age of diagnosis 63 years and 75 years for colorectal and bladder cancer, respectively.[1] After ostomy surgery, a major treatment option,[1] patients often encounter significant symptoms and complications (e.g., dehydration, infection) and wound care problems.[3,4] These symptoms and complications are associated with reduced quality of life (QOL)[5-7] and high rates of morbidity and mortality.[8,9] Poor symptom management is also a primary reason for emergency room visits,[10-12] hospital readmission,[4,9,13] and high costs of care for patients with ostomies.[4] There has been limited research to support cancer patients and caregivers to manage symptoms, improve QOL, and reduce preventable hospital visits and their related costs while CBC patients transition from in-patient care to post-treatment self-care at home.

To address these issues, our team has developed a web-based mHealth symptom and complication monitoring and self-management program for CBC patients with ostomies and their family caregivers, known as PRISMS. PRISMS is a personalized/customized mHealth program that integrates patient reported-outcomes (PRO) measures and technology in enhancing program relevance and usefulness, and improving human-technology interaction and information delivery, all of which predict use of technology-delivered programs.

PRISMS aims to provide monitoring, education, skills training, and social support to ameliorate the complex, interrelated symptoms and complications, and ultimately, improve QOL. PRISMS includes modules addressing ostomy care, the *most common* complications (e.g., dehydration, skill problems) and related

physical and psychosocial symptoms (e.g., fatigue, sleep disturbance, emotional distress, and sexual dysfunction), and safe physical activity for speedy recovery (while preventing hernia and falls). PRISMS integrates PRO (e.g., fatigue) and objective data from wearable devices (smart bottle and smart scale that monitor fluid intake and loss) to provide continuous monitoring of patients' symptoms and complications after they are discharged home. PRISMS triages patient care based on the monitoring data that indicate severity of their symptoms and complications. Patients and caregivers will self-monitor and manage at home for mild and moderate symptoms but be referred to professionals (e.g., wound and stoma nurse) when the patient experiences severe symptoms or significantly worsened symptoms. PRISMS also provides moderated online forum to promote peer support among study participants who face similar challenges, as well as "Let's Chat" to facilitate professional support.

1.3 Purpose and Rationale

This is a pilot randomized clinical trial (RCT) using mixed methods. We will examine the feasibility of PRISMS by conducting a two-armed pre-post pilot RCT study and interviews to obtain feedback from participants who use PRISMS. Study participants - twenty CBC patients with new ostomies and their caregivers (N=20 dyads, i.e., 40 individuals) - will be randomly assigned to either the PRISMS or usual care groups.

2.0 STUDY OBJECTIVES AND ENDPOINTS

The objective of this pilot randomized clinical trial is to test the feasibility of the innovative PRISMS program to enhance personalized supportive care for cancer patients and caregivers during care transition. The aims that will help gather preliminary data for a larger definitive trial are listed below. The indicators of feasibility will include recruitment, enrollment and retention rates as well as automatic recorded online activity comprising navigation time, number of logins, utilization of program sections, which we will collect the data using administration log and study website.

The study outcome, *Quality of life* (QOL), will be assessed at T1 and T2 using the 27-item Functional Assessment of Chronic Illness Therapy general scale (FACT-G).[94] We will measure general QOL and physical, social/family, emotional, and functional subdomains.[95] Caregivers will report QOL using the spouse's version of FACT-G with slightly modified wording.[96] We will use the PROMIS measures of fatigue, pain, sleep disturbance [97-100] and Cancer Anxiety[101] and Depression[102] to assess patient and caregiver *symptom distress* at T1 and T2. We will also collect participants' demographics (age, race/ethnicity, income, education) and patient treatment information at T1. At T2, we will collect quantitative data on participant satisfaction of and comfort with using PRISMS.

2.1 Primary Objective

To examine the feasibility of delivering PRISMS to patients and caregivers (as assessed by the recruitment, enrollment, and retention rates, and satisfaction

with and perceived ease of use of PRISMS).

2.2 Secondary Objectives

To estimate the magnitude of benefit of PRISMS. We hypothesize that, compared with the patients receiving usual care, the PRISMS users will report (1) greater improvement in their primary outcomes of QOL (overall, physical, emotional, and social QOL); and (2) fewer post-treatment care services related to stoma complications (e.g., ER visits, readmission, use of healthcare providers) from between T1 and T2.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients must (1) have been surgically treated for bladder or colorectal cancer; (2) have a newly created ostomy within the past 4 weeks, and (3) have a caregiver who is willing to participate in the study. The caregiver must (1) be 18 years and older, (2) be identified as the primary caregiver by the patient. We will also recruit 3-5 providers who provide direct post-surgical care to CBC patients to provide feedback on the PRISMS. Providers, patients and caregivers will be recruited from the LCCC urologic (GU) and *gastrointestinal (GI)* oncology in- and out-patient units.

3.2 Exclusion Criteria

Patients and their caregivers will be excluded if they are unable to read, speak, or understand English. Have other cancer excluding non-melanomatous skin cancer or have cognitive impairment.

4.0 STUDY PLAN

4.1 Schema

We will recruit patients and caregiver dyads based on procedures used successfully in the past.[83,93] After PRC and Institutional Review Board (IRB) approval, we will inform the health care providers working at the GU and GI units and obtain their permission to display the flyers of our PRISMS study (with our contact information) on the information board at the units.

A research team member will meet the patients who express interest in the PRISMS study by calling the research office or informing the professionals on the UNC LCCC in-patient GU or GI unit prior to their discharge home. The research team will provide study information, answer questions, screen the patient and caregiver for eligibility and willingness to participate, obtain informed consent, and collect baseline (T1) data (demographics, QOL, and symptom distress). The coordinator will then schedule a home visit to install PRISMS within 48 hours of discharge and train participants to use the study devices. Patients and caregivers

will use the PRISMS for 3 months—the period of time that patients have the highest risk for complications and related ER visits and readmission. Participants will be instructed to synchronize their devices daily. Participants will be contacted via telephone and email after 3 months to conduct the follow-up interview (T2) and collect the devices.

4.2 Duration of Study

The study will be conducted for 3 months among CBC patients and caregivers. There will be a survey at the beginning and end of the 3 months. The providers will be in the study one time for about 30-45 minutes to complete an interview.

4.3 Study Details

The coordinator will meet the patients who express interest in the PRISMS study by calling the research office or informing the professionals the GU or GI units prior to their discharge home. (Note: However, the clinician Co-Is and the PI will meet I early September to explore the possibility and procedure of enrolling potential participants prior to surgery. Once we have the details we will modify the study protocol immediately.) The coordinator will provide study information, answer questions, screen the patient and caregiver for eligibility and willingness to participate, obtain informed consent, and collect baseline (T1) data (demographics, QOL, and symptom distress). The coordinator will then schedule a home visit to install the PRISMS within 48 hours of discharge and train participants to use the study devices. Patients and caregivers will use the PRISMS for 3 months—the period of time that patients have the highest risk for complications and related ER visits and readmission. Participants will be instructed to synchronize their devices daily. Participants will be contacted via telephone and email after 3 months to conduct the follow-up interview (T2) and collect the devices.

Our project coordinator will identify potentially eligible patients and caregivers and introduce to them the PRISMS study and answer any questions they may have via in-person meeting (before discharge) and via telephone (after discharge). Potentially eligible patients and caregivers will be provided study brochures and introductions, written or telephone informed consent (whichever is the most convenient for participants) will be obtained from all patients and their caregivers prior to any research activities. After informed consent, patients and caregivers will complete their baseline assessment of quality of life and symptom distress. The project coordinator will then schedule for a home visit to install the study devices within 48 hours after patient discharge. The coordinator will teach participants how to use the devices and synchronize data daily. Patients and caregivers will then be encouraged to use PRISMS as scheduled. The standardized schedule is twice a day for 3 days, then daily for two weeks, and finally weekly for the rest of the study. But the assessment schedule can be reset if new symptoms and complications appear or existing symptoms and complications worsen. That is, if the patient experiences severe symptoms, participants will be automatically directed to use PRISMS more often. The synchronization between the iPAD and wearable devices (Fitbit, smart scale, and smart bottle) is designed to be a 1-click process to ease PRISMS use for elderly participants because colorectal and bladder cancer disproportionately influence older people.

The follow-up assessment will be conducted via telephone approximately 3 months after baseline. Following T2 data collection, all patients and caregivers will be interviewed to obtain qualitative evaluation of their experiences using PRISMS and suggestions for improving PRISMS and the study design.

4.4 Expected Risks

There is minimal risk to participants. Compared to patients receiving routine post-surgical care at home, PRISMS will enhance symptom monitoring and personalized management. We will integrate the PRO measures and data from wearables into PRISMS to enhance routine symptom monitoring. If patient's symptoms and health conditions become severe or worsened, professional providers (e.g., the surgical oncology nurse navigator, residents) will be informed via email, which will prompt necessary medical intervention and professional follow-ups. Patients and caregivers will also be reminded to contact patients' providers directly if needed and to call 911 for emergencies. The research team is comprised of urologic and surgical oncologic surgeons and a medical oncologist. The team will meet monthly (or as needed) to review any potential adverse events and provide professional guidance on how to handle potential risks.

While the risk of this study is minimal, patients and caregivers will be informed that they can withdraw from the study at any time. All data collected will be saved on password-protected, encrypted shared drives on UNC campus. Qualitative data will be directly transcribed and coded; whereas quantitative data will be collected and stored using the NC TraCS-managed Redcap. Each participant will receive a unique identifier that will be used to store the de-identified quantitative and qualitative data, and to maintain participant anonymity. Data will be stored separately from patient identifying information on the secure UNC network servers. All data will be available only to study personnel with password protection.

4.5 Removal of Patients from Protocol

Participants can withdraw from study at any time.

5.0 TIME AND EVENTS TABLE

5.1 Time and Events Table

This study will recruit participants over a 2-month period (or until we successfully recruit 20 patient-caregiver dyads and 3-5 clinicians). Patient and Caregiver will be interviewed at the beginning and again at the end of 3 months. Each interview will last 30-45 minutes.

	Aim 1	Aim 2			
	Feasibility	**Baseline**	**PRISMS (3-**	**Follow-up**	**Post-pilot exit interview**
Recruitment	**x**				

Screening	x				
Informed Consent	x				x
Interviews	x				x
QOL[1]		x		x	
PRO symptoms		x		x	

6.0 UNANTICIPATED PROBLEMS

6.1 Definition

This study involves minimal risk to the participants.

As defined by UNC's IRB, unanticipated problems involving risks to study subjects refers to any incident, experience, or outcome that:

- Is 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;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

6.2 Reporting

Any UPIRSO that occurs during the conduct of this study and that meets all three criteria listed in 6.1 must be reported to the UNC IRB using the IRB's web-based reporting system.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design

This is a pilot randomized clinical trial (RCT) using mixed methods. We will conduct a two-armed pre-post pilot RCT study and interviews to obtain feedback from participants who use PRISMS. Study participants - twenty CBC patients with new ostomies and their caregivers (N=20 dyads, i.e., 40 individuals) - will be randomly assigned to either the PRISMS or usual care groups.

7.2 Sample Size and Accrual

We plan to recruit 20 patients with recent ostomy (within 4 weeks) and their caregiver (with a total of 20 patient-caregiver dyads and 40 individuals) and 3-5 health care providers. Based on previous experiences, we anticipate we will achieve data saturation among these participants. We claim such a study as

feasible if and only if both (i) recruitment rate (p) and (ii) retention rate (q) are large enough. More specifically, this is to test the following hypothesis: H0: p <= 65% or q <= 65% vs H1: p >= 80% and q >= 80%. We will claim the study feasible (high recruitment rate and high retention rate) if we reach 29 or fewer patients/dyads to recruit 20 dyads, AND more than 14 (>= 15 out of 20) participants remained in the study. This study reaches 76% power at alpha level 0.10. In addition, we will estimate the proportion and associated 95% confidence interval of patients' satisfaction with and perceived ease use of PRISMS. With 10 couples in the PRISMS arm and expected satisfaction rate of 70%, the width of the 95% CI will be around 0.58 (0.29 for 1-side width).

7.3 Data Analysis Plans

The feasibility of successful delivery of PRISMS will be measured using indicators such as recruitment and retention rates. Analysis of these primary indicators are described above.

Appropriate descriptive statistics will be calculated for other indicators of feasibility, quality of life; general, and physical, social/family, emotional, and functional subdomains, for participants and partners, by time point (T1, T2), and by group, and patient's health care services utilization (e.g., clinic visits, ER visits, and readmission) by group. This sample size (10 in each group) will ensure 80% power to detect a large effect size of 1.15 at the one-sided 0.05 significance level using a two-sample t-test to compare the difference in pre-post change (from T1 to T2), or mean level at T2 (if an outcome is only measured at T2), of a given outcome between the two intervention groups.

Appropriate exploratory analyses (e.g., trajectory analysis of frequently measured PRO outcomes), for the purpose of generating hypotheses, may be conducted.

All analyses will be conducted using an intention-to-treat approach, in which all randomized participants will be analyzed according to their assigned group, regardless of the extent of intervention actually received. Due to the fact that this is an exploratory proof-of-concept study, rather than a confirmatory study, we will not adjust for multiplicity when computing the CIs in conducting comparisons. Unless otherwise specified, all tests will be one-sided at an alpha level 0.05. All analyses will be conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

7.4 Data Management/Audit

Data will be collected at baseline (T1) and follow-up (T2) surveys and post-exit interview by the research assistant assigned to data collection. We will use RedCap to store all of our data. Feasibility of PRISMS will be measured using indicators such as recruitment and retention rates, and automatic recorded online activity comprising navigation time, number of logins, utilization of program sections. We will collect the data using administration log and study website.

7.4.1 Data Management

Study ID numbers will indicate the identities of subjects, and this information will be accessible only to the study investigators. All questionnaires will bear study ID

numbers only. Research team staff will conduct all telephone survey sessions in a private workstation in a private office designated to the research team. The telephone surveys will be recorded and reviewed by the PI, project coordinator, research staff at the project office to ensure adherence to the study protocol as well as data completeness and accuracy. We will randomly check at least 20% of the recordings against completed data for adherence to protocol, data completeness, and accuracy.

REDCap online database will be managed by the TraCS Clinical Research Data Management Service. NC TraCS is a key initiative of the Biomedical Informatics core of the UNC-Chapel Hill CTSA. The purpose is to provide a system and associated support resources, to enable efficient and high-quality collection and management of research data that is standards-based in design, development and implementation. Standard features of electronic clinical research data management systems are available in the web-based systems provided with the service. These include interactive data entry with real-time field validation, lab data imports, audit logs to record database modifications, database integrity checks, security (in logins, permissions based on need, and encryption), reporting, forms inventory, and exports to common statistical packages for analysis. Logging tracks all data entered in REDCap so that it can be traced back to the person who entered it. No data can be changed without showing who has made the changes. This allows the study team to ensure there is security and integrity of the data collected and submitted, there are controls surrounding this aspect. REDCap also provides for principle investigator to sign off on the data, as required in FDA studies. Although users can modify data based on their permissions, they cannot delete the subject or history of that subject. Requests to delete a subject must be made to the REDCap system administrator. Our database system provides for secure web-based data entry with the data stored on servers that staff at NC TraCS maintain. The data is encrypted during transmission. The servers are located in a secure campus area with all the appropriate physical security measures in place. The web and database servers are monitored by the TraCS IT staff, patched frequently, and scanned by a third-party vendor to ensure that they are protected against known vulnerabilities. The scanning application is the standard service for the entire campus. Access is by individual user id, and is restricted to the forms and/or functions that the user needs to have. The applications themselves are written using open source tools, and have also been scanned by campus security office to ensure that the applications also are protected from known exploits. The data is backed up to electronic media on a daily basis. The electronic media is secured by ITS stored in a secure area separate from the servers.

The study website for PRISMS and NCI landing is hosted and maintained by the Communication for Health Applications and Interventions (CHAI) of the UNC Lineberger Comprehensive Cancer Center. The web activity data of all participants will be deidentified (using randomly assigned user IDs) and automatically tracked via a built-in feature of the study website. The de-identified web activity data from the PRISMS website and the NCI website landing page at CHAI will be automatically electronically transferred through SFTP to the research office at the School of Nursing on a weekly basis.

All administrative data (including randomization, referral data) will be centrally managed using REDCap at the PI's research office at the School of Nursing and accessed only by the study investigators and research staff. These administrative data will be managed separately from the deidentified, password protected, encrypted and securely transferred data including surveys and web activity data. The PI and project coordinator will examine weekly the accuracy of the data files and completeness of the data.

The data collected from this study will help us to design and conduct a definitive trial to examine the efficacy of PRISMS, a potentially scalable intervention that can be disseminated through oncology clinics nationwide to enhance post-treatment care for CBC patients with ostomies and their caregivers. All data will be deidentified and saved in secure encrypted shared folder on UNC server. All identifiable data will be deleted from redcap and other sources following IRB instruction and data safety policies.

7.4.2. Data Monitoring/Audit.

This study is of such low risk. With a primary outcome of change in quality of life (QOL) between the PRISMS and the usual care control groups, there would not be anything significant to provide to the DSMB that might signal a reason for the DSMB to stop a study. However, we will implement a data and safety-monitoring plan to ensure the safety of participants as well as the validity and integrity of the data. The data monitoring plans are as follows:

Oversight for this study will be provided by the PI with input and advice from the team. An Adverse Event Monitoring Committee will be formed to oversee the conduct of the study. Chaired by the Dr. Song (PI), the committee will be comprised of all of the Co-investigators. Dr. Song will chair the committee, which will meet as needed to review the activities of the study including management, personnel, recruitment, performance, and any emerging problems. The research staff will ensure all entry criteria are met prior to the initiation of the protocol and all study procedures and reporting of adverse events and unanticipated events is performed according to the IRB-approved protocol. Any actions taken and associated follow-up activities will be recorded in the study database. All intervention-related adverse events will be reported to the PRC and IRB within 3-7 days. The PI and the Adverse Event Monitoring Committee will assess the level of risk from adverse events as mild (no interference in usual activities); moderate (some interference in usual activities); or severe (usual activities were significantly interrupted). The PI and the Adverse Event Monitoring Committee will rate the assessment of attribution to the study as not related, unlikely, possible, probable, or definite.

Serious Adverse Event (SAE)/***Serious Unanticipated events (***SUE) reviewing and identifying. The PI will convene weekly meetings with the research staff to review project progress, subject accrual, follow-up, and any anticipated or unanticipated AEs. The PI and project manager will be responsible for monitoring study processes and ensuring that AEs and UEs are reported immediately to the Adverse Event Monitoring Committee, the Independent Monitor, the IRB at LCCC and UNC-CH.

The study Independent Monitor will receive the aggregated progress information for reports quarterly compiled by the Adverse Event Monitoring Committee to determine if any of the study procedures should be altered or stopped. The Adverse Event Monitoring Committee, including 3 nurse scientists, a psychologist, 3 physicians, 1 statistician, and all research staff, will review any adverse events, safety concerns or problems (e.g., patients' symptoms of distress), appropriateness of strategies of handling these AEs and UEs and needed improvement in study procedures, in addition to the assessment of study performance related to subject referral, recruitment and retention, protocol adherence, and the quality of the data.

(f) SAE/SUE Reporting.

The PI (Dr. Song), Co-Is, and the research staff will perform continuous and close monitoring with prompt reporting of AEs to the LCCC PRC and IRB at UNC-CH. The PI, Co-Is and staff will comply with the UNC guidelines for reporting AEs that require investigators to report any AEs that are unexpected, fatal or life threatening to the IRB using standard forms within 24 hours of the incidents. Additionally, the PI will report to the NIH within 24 hours the SAEs and actions, if any, taken by investigators or the IRB as a result of the event or its continuing review.

8.0 STUDY MANAGEMENT

8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol prior to consenting and enrolling any participants.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the feasibility study, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

8.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form

8.3 Registration Procedures

Patient enrollment with be captured in RedCap which is password protected.

8.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.4.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

8.4.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for LCCC Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

8.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.

- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore® (or other appropriate database set up for the study), and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report UPIRSO.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO: Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB (see section 6.1) must be reported by the Study Coordinator using the IRB's web-based reporting system.

8.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

8.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on

Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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10.0 APPENDICES

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