Mastectomy Flap Temperature and Clinical Implications	
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Participating Institution(s): ***Wake Forest Baptist Comprehensive Cancer Center***
Version Date: 4/07/2022
Amended:

Confidential

ClinicalTrials.gov: NCT05395936

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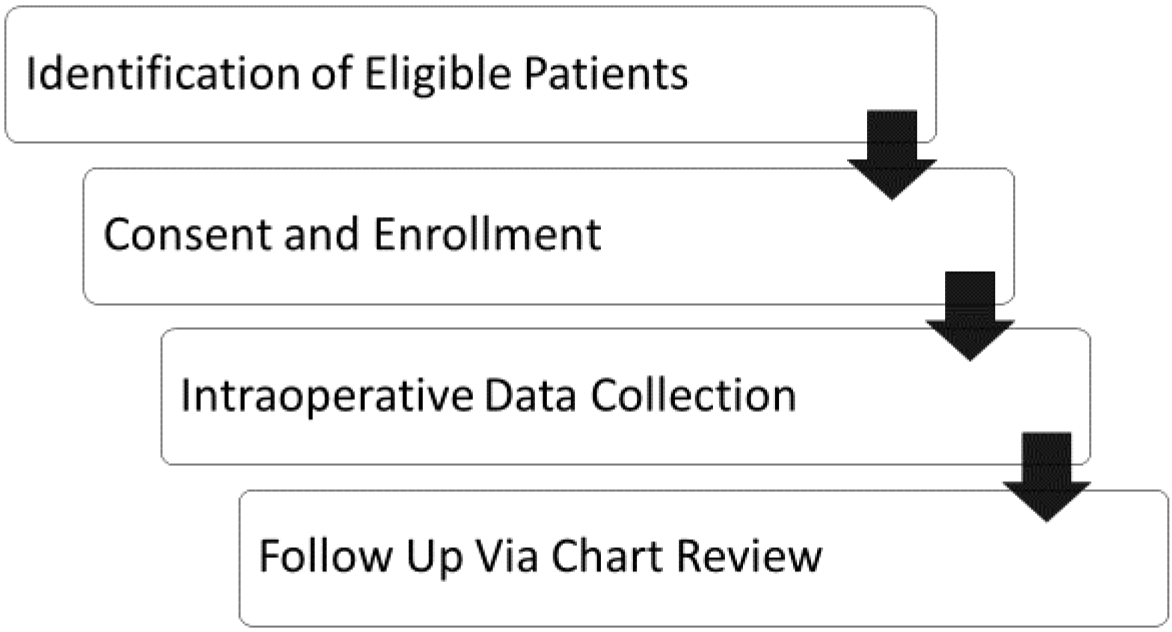
SCHEMA


Identification of Eligible Patients
Consent and Enrollment
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1.0 Introduction and Background

Breast cancer is the most common cancer diagnosis of women in the United States, making up 25% of all cancer diagnoses.[1,2] Among those undergoing surgical intervention, 50% have a mastectomy. Within this group of mastectomy patients, up to 50% opt for breast reconstruction.[1] The most recent surgical trend data from the American Society of Plastic Surgeons shows that almost 90,000 breast reconstructions in the United States were implant-based in 2019, making up approximately 80% of all breast reconstructions.[3] Along with the upward trend in implant-based breast reconstruction, there remain high rates of surgical complications. The rate of surgical site infections is higher in implant-based reconstruction as compared to autologous reconstruction. The implant-based reconstruction infection rates range from approximately 6-28%, while the infection rate for autologous reconstruction is 5% and 0.1-1.5% for breast augmentation.[4] The sequela of surgical site infection can place a significant burden on the patient and healthcare system and can even delay oncologic care in some cases.[4] Numerous protocols and anecdotally based methods are often applied in efforts to reduce surgical site infection. Despite these attempts, there remains a large gap in evidence-based medicine on how to successfully decrease risk of surgical site infection in implant-based breast reconstruction.

Clinicians often note that both intraoperatively, and months postoperatively, mastectomy flaps are clinically cool to the touch, but mastectomy flap temperature has not been objectively studied.[5] The importance of maintaining normothermia during surgery has been well established in both anesthesia and surgical specialties literature over the past twenty years.[6–10] The combinations of impaired thermoregulatory control from the anesthesia and exposure to cool operating rooms makes most surgical patients hypothermic (defined by anesthesia practitioners as being less than or equal to 36 degrees celsius.[6]) Wound temperature is heavily reliant on, and correlated with, core body temperature, as the wound temperature is higher in normothermic patients than in hypothermic patients.[6] The clinical impact of this has most markedly been observed in the colorectal specialty in which a study found that patients with mild perioperative hypothermia had three times as many surgical-wound infections as the normothermic patients.[8] As stated above, implant-based reconstruction after mastectomy consistently has higher rates of infection than other implant based procedures or even autologous breast reconstruction. This is often attributed to the decreased mastectomy flap perfusion that becomes solely reliant upon the subdermal plexus after a total mastectomy ultimately leading to impaired blood flow and subsequent impairment in immune function.

Hypothermia causes vasoconstriction leading to immune dysfunction among t-cell-mediated antibody production, chemotaxis, phagocytosis of granulocytes, motility of macrophages, and non-specific oxidative bacterial killing by neutrophils.[6,8] The decrease in killing by neutrophils occurs due to decreased blood flow, in turn decreasing the oxygen tension of mastectomy flaps. This causes a decreased production of both oxygen and nitrous free radicals, which is an oxygen-dependent process. This oxidative killing process is responsible for many gram positive organisms such as Staphylococcus aureus, which is the most frequently isolated organism in breast implant infections.[6,11,12] Hypothermia and impaired blood flow in the first few hours of the case can render preoperative antibiotics less effective or in some cases ineffective. Furthermore, after surgery core hypothermia can take up to five hours to resolve, which leads to bacterial fixation and risk for infection.[6] An animal in vivo study demonstrated reduced resistance to test infection suggesting that temperature plays a vital role in immune function.[6]

The blood flow has also been described in the setting of temperature dependent blood flow in flaps. Most surgeons assess the flaps subjectively by observing temperature, capillary refill and overall appearance of the flap. While often utilized, it is not reliable or reproducible to rely on the intuition and experience of the surgeon. In an animal study, it was found that skin perfusion often increases in the first 24-48 hours after surgery. [13] The researchers found that if intraoperatively the flap is heated to 42 degrees Celsius it mimics the microcirculatory environment encountered at 24-48hours post-surgery.[13] The warming of the flap can stave off the deleterious effects of the vasoconstriction. Vasoconstriction has been found to create a hyperadrenergic state causing further vasoconstriction, perpetuating the cycle of hypoperfusion and lower temperatures. The lower temperatures have been found to inhibit nitrous oxide secretion causing overexpression of alpha-2c adrenergic receptors which amplifies the vasoconstrictive effects. In addition, thermoregulatory vasoconstriction significantly decreases subcutaneous oxygen tension. The incidence of wound infections correlates with subcutaneous oxygen tension.[6]

Given the increasing quantity of literature that concludes that core temperature is an independent risk factor for increased complications there has been an attempt to control this by preconditioning the mastectomy flaps. Five to thirty percent of mastectomy skin flap necrosis is often cited in the literature.[14] While in its infancy, the handful of studies that have attempted this intervention have found promising outcomes. One review article examined the concept of thermal preconditioning which was defined as “local or systemic supraphysiological heating of an organism or specific organ before an environmental insult.”[10] It has been established that through heat exposure there is an increase in heat shock proteins (HSP). Specifically, HSP-32 can catalyze hemoglobin to biliverdin and iron with a byproduct of this reaction being the local release of carbon monoxide. Carbon monoxide is a potent vasodilator that causes an increase in vascularity to the specific preconditioned area. HSP-70 is also suspected to play a role in vasodilation through inducing production of nitrogen oxide synthase (iNOS).[10] Protective effects of HSP and preconditioning has been demonstrated in multiple other organs like kidneys, bone, heart and liver.[15] This physiologic reaction was examined in a randomized control trial through local supraphysiologic heating of breasts that were to undergo mastectomy the following day. A heat source of 43 degrees Celsius was applied for 30 minutes 3 times with a 30-minute rest between the repetitions. It was found that those who did not undergo preconditioning had 35% necrosis rate of mastectomy flaps, while those who did undergo preconditioning experienced 26% necrosis rate of mastectomy flaps.[14]

To date there has been no study that has examined the feasibility of objectively quantifying the temperature of mastectomy flaps, or that has studied the relation between flap temperatures and core body temperature. This pilot study seeks to establish foundational evidence related to the feasibility of measuring temperatures of mastectomy flaps and to quantify the relation between flap and core temperatures. Specifically, we hypothesize that 1. we will be able to obtain consent from at least 60% of women undergoing therapeutic or prophylactic mastectomy (unilateral or bilateral, with reconstruction) to obtain flap temperatures intraoperatively, both pre- and post-mastectomy (note that core body temperature is measured continually as a usual aspect of intraoperative procedure, and thus does not require specific additional consent); 2. we will be able to successfully measure flap temperatures in 4 quadrants of relevant breast tissue (one or both breasts, depending on unilateral vs bilateral surgery) at each time point on at least 90% of those who do consent; and 3. average mastectomy flap temperatures will be significantly lower than core body temperature in this pilot sample.

Additionally, we will explore the relation between average mastectomy flap temperature and number and degree of post-surgical complications for up to 90 days post-surgery, to examine whether patients with cooler mastectomy flaps intraoperatively have increased surgical complications compared to patients with warmer flaps. While there is a possibility that the presence or absence of cancer can affect surgical complication rates, we do plan to include patients undergoing both therapeutic and prophylactic mastectomy in this study. When performing data analysis, complications are recorded by breast rather than by patient allowing us to note which breasts undergo mastectomy for therapeutic reasons and which are prophylactic.

If we are successful in showing feasibility in our primary objectives, we hope that these pilot data will ultimately aid in future, large interventions designed to warm or precondition mastectomy flaps in efforts to optimize surgical outcomes for implant based breast reconstruction surgeries.

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 Quantify the proportion of eligible women approached who consent to intraoperative (pre and post mastectomy) measurement of mastectomy flap temperatures in each of 4 quadrants of each relevant breast (i.e., unilateral or bilateral procedure).
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2.1.2 Quantify the proportion of patients upon whom the surgical team is able to obtain intraoperative flap measurements from each of 4 quadrants on each relevant breast pre- and post-mastectomy and pre-implant.

2.2 Secondary Objective(s)

2.2.1 To measure mastectomy flap temperatures in 4 quadrants pre-mastectomy, following mastectomy, and pre-implant, and compare average flap temperature to average core body temperature.

2.3 Exploratory Objective(s)

2.3.1 Quantify relationship between flap temperatures and incidence of mastectomy surgical complications within 90 days of surgery.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Scheduled for unilateral or bilateral mastectomy with implant based breast reconstruction within the Wake Forest Baptist Health System.

3.1.2 Aged 18 or older.

3.1.3 Ability to understand an IRB-approved informed consent document (either directly or via a legally authorized representative).

3.2 Exclusion Criteria

3.2.1 Those who are male.

3.3 Inclusion of Women and Minorities

Women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study. Because they do not get implant-based reconstruction (and have a comparatively low risk of breast cancer) men will be excluded from this study.

The study consent form will also be provided in Spanish for Spanish-speaking participants.

4.0 Study Outcomes and Study Measures

4.1 Primary Outcomes

5.1.1 The proportion of eligible women who consent to having mastectomy flap temperatures measured during surgery will be computed by dividing the total number of eligible women screened by the number of these women who consent. We will compute a 95% confidence interval around this proportion.

5.1.2We will compute the proportion who successfully have all relevant flap temperatures measured (this will either be 12 or 24 total expected flap temperatures: 4 quadrants, at three time points- pre and post-mastectomy and pre-implant placement; one or both breasts), and we will compute a 95% confidence interval around this proportion.

4.2 Secondary Outcome

- Mastectomy flap temperatures will be measured using a 22 gauge myocardial temperature sensor (Smiths Medical). Temperatures will be recorded in degrees Celsius. Core body temperature will also be collected.

4.3 Exploratory Outcome

Mastectomy flap compromise/wound breakdown (major vs. minor complication) will be assessed over 90 days following surgery. We will document the following through chart review including but not limited to infection, ischemia, seroma, hematoma, and wound dehiscence.

5.0 Study Design and Study-Related Activities

5.1 Design

- This is a prospective observational (non-randomized) study that will collect data intraoperatively and assess exploratory outcomes up to 90 days post-surgery through chart review

- Information that will be stored within a secure database will include demographic data, details of medical, surgical, and social history, oncologic history, and surgical data surrounding the mastectomy and reconstruction until 90 days post operatively through chart review. The only piece of identifying data that will be collected is the medical record number in order to allow prospective chart review for the surgical outcome measurements.

All patients of the age of 18 or above that are scheduled for mastectomy and implant-based breast reconstruction and who meet our remaining eligibility requirements will be screened for our study and enrolled if they consent. If the patient meets eligibility requirements a study team member will reach out to them via a telephone call prior to their surgery date. If the patient expresses an interest in taking part in the study a study team member will meet with them in the pre-op holding room the day of surgery to obtain written informed consent. To address our feasibility objectives, we plan to record the medical record numbers of patients who decline participation in the study. Clinical data and patient information will be entered into an encrypted, password protected database by approved study personnel. The type of information that will be collected and entered into the database will include (but not be limited to) that shown below in Table 1. The database will be updated with pertinent information for each subject after each surgery and postoperative visit on an intermittent basis. The intraoperative data points will be collected through the use of a myocardial temperature probe (See Section 6.1.1 and Figure 1) introduced into the 4 quadrants. This is a disposable temperature sensor. One sensor will be utilized for each patient. The flap temperatures will be collected by the research staff. There will be a hard stop on the probe at 4mm of depth in order to assess the temperature of the subdermal plexus upon which the mastectomy flap will be perfused.[11,12,16] Core temperature will be assessed simultaneously using standard-of-care anesthesiologist-mediated methods involving a temperature probed placed in the nasopharynx.[9] For this study specifically, core temperatures will be recorded at the same time intervals as the localized mastectomy flap temperatures are obtained.

OF NOTE: Due to risk of puncturing the implant with the myocardial temperature sensor post implant placement, flap temperatures at this time point will **not** be collected. If a pre-implant temperature is missed, post-implant flap temperatures are not allowed.

5.1.1 Smiths Medical Myocardial Temperature Sensor

A myocardial temperature sensor will be used to obtain flap temperatures (Figure 1). The sensor is in a 22 gauge needle and is 8mm in length. This is a disposable temperature sensor. One sensor will be utilized for each patient. The flap temperatures will be collected by the research staff. There will be a hard stop on the probe at 4mm of depth in order to assess the temperature of the subdermal plexus upon which the mastectomy flap will be perfused.[11,12,16]

Figure 1. Smiths Medical Temperature Probe

5.1.2 Temperature-Related Supportive Care

The surgical and anesthesia literature defines 36 degrees Celsius or less as hypothermic and 38 degrees or greater as hyperthermic.[6] These values will also be used for the mastectomy flap temperatures. The mastectomy flap temperatures that are below 36 degrees are considered to be physiologically hypothermic and anything above 38 degrees Celsius is physiologically hyperthermic. However, the standard of care is to only treat the core temperature of the patient, which will be what we adhere to in this study. If the patient is hypothermic standard intraoperative protocols such as increasing the room temperature, turning on the Bair hugger and running warm fluids will be performed to correct hypothermia. If the patient is hyperthermic, running cool fluids, turning off the Bair hugger and decreasing the room temperature will be implemented for correction of hyperthermia.

Table 1: Data Points to be Collected	
Preoperative	- MRN - Age - BMI - Smoking status - Diabetes Mellitus - Neoadjuvant radiation - Neoadjuvant Chemotherapy - Tumor type and stage
Intraoperative	- Mastectomy weight - Size of tissue expander or implant placed - Number of drains placed - Temperature collection: - Pre-mastectomy - core temp and flap temp in 4 quadrants

	- Post-mastectomy - core temp and flap temp in 4 quadrants - Pre-implant placement – core temp and flap temp in 4 quadrants
Postoperative	- Duration of drains - Seroma formation - Infection within 90 days - Antibiotic administration postoperatively, up to 90 days - Mastectomy flap necrosis within 90 days

5.2 Overview of Study-Related Activities

	Pre-Study	Intraoperatively	Post-Operative Clinic Visit	Up to 90 days post-operatively
Informed consent	X			
Temperature Collection		X		
Demographic Data				X
Chart Review Items				X
Adverse event evaluation (CTCAE v5.0)		X	X	X

5.4 Duration of Follow Up

For the purposes of this research study, patients will be followed for 90 days after surgery for adverse events from the introduction of the probe to collect temperature and for exploratory outcomes.

5.5 Off-Study Criteria

- The patient completes all study activities, and no further follow-up or data collection is required.
- The patient withdraws from all study activities and further data collection.
- The condition of the patient changes in a manner that it is determined that it is no longer in the patient's best interest to continue the study in the opinion of the investigator.
- Patient lost to follow-up
- Death

6.0 STATISTICAL CONSIDERATIONS

6.1 General Design Issues

This is a non-randomized prospective observational pilot study.

1. **Primary Hypotheses:** We hypothesize that at least 60% of eligible patients will consent to having flap temperatures measured intraoperatively, and that we will successfully measure all relevant temperatures (12 per breast) on at least 90% of those consenting. Both of these measures must be achieved to deem a future study feasible.
2. **Secondary hypotheses:** We hypothesize that we will observe a significant difference between average mean flap temperature and average core body temperature.
3. **Exploratory analyses**: We will describe post-surgical complications over the 90-day post-surgery period as frequencies.

6.2 Sample Size

Our target sample size of 30 eligible patients, expected to be accrued over a period of 3-6 months, is based on our primary goals of examining feasibility measures to inform the design of a larger intervention trial. An n of 30 will provide reasonably tight estimates of our parameters of interest. We will be able to estimate these proportions within 19.4% (for the lower CI bound; the window is smaller for the upper bound) using a two-sided 95% confidence interval. If the consent proportion is below 40.6% (fewer than 12 women consenting out of the 30 eligible), or the success in measuring all flap and peri-incisional temperatures occurs in fewer than 65% of the expected n=18 (i.e., fewer than n=11 women out of the starting pool of 30), we will conclude that a larger study of flap temperatures may not be feasible.

Power calculations for a subsequent larger study will be based on clinically and statistically meaningful differences between average flap temperatures and core body temperatures and will be informed by measures obtained in this pilot.

6.3 Data Analyses

This study will provide quantitative data on consent (proportion of all eligible patients approached who consent to having flap temperatures measured intra-operatively), and on ability to successfully measure all 12 flap temperatures (per breast) on patients who have consented.

We will calculate 95% confidence intervals for each of the above feasibility measures to determine the range of estimates that are consistent with our data. We will use one-sample tests of binomial proportions to compare the consent and successful measurement proportions to the hypothesized values of 60% and 90%, respectively.

We will examine intra-individual variability in flap temperature measurements by quadrant and by breast; we expect these sources of potential variability to be weak, controlling for time point of measurement (pre vs post mastectomy vs pre-implantation). We will derive average flap temperatures for each of the three time points separately. We will compare average flap temperatures at each of the three time points during surgery to average core body temperature at that time, using paired t-tests for the differences in means in a single sample. Our hypothesis is that, across all three time points, average flap temperatures will be lower than average core body temperatures, and that as time goes on during surgery, from pre- to post-mastectomy to pre-implantation, we expect average flap temperatures will be lower than average core body temperatures by a larger degree, as we expect flap temperatures to cool more quickly during surgery than overall body temperature.

In our exploratory analyses, we will document the occurrence and major and minor wound/surgical complications over the 90-day period following surgery and will examine whether there is a relation between the number of such complications per patient and 1. the patient's magnitude of difference between average flap temperatures and core body temperatures, and 2. the patient's absolute average flap temperatures .

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7.0 Adverse Events List and Reporting Requirements

7.1 Adverse Event List for insertion of myocardial temperature sensor

The myocardial temperature sensor is the size of a 22 gauge needle. This is a similar size of the needles used to inject local anesthetic into the skin for postoperative pain control, as well as the injection isosulfan blue administered by surgical oncology. This will not affect the aesthetic outcome or increase the risk for post-operative complications. Though the risk of harm or discomfort that comes from participation in this study is no more than what is anticipated in a typical intraoperative mastectomy experience and post-surgical course following mastectomy with breast reconstruction. Adverse events that may occur include bruising or cellulitis at the location of the probe insertion. This could be indistinguishable from other trauma inflicted by the surgery itself. In an effort to ensure appropriate data collection of adverse events, efforts will be made to ensure the temperature measurements will be taken in generally standardized locations of all 4 breast quadrants.

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

'Expectedness': AEs can be 'Unexpected' or 'Expected' (see Section 8.1 above) for expedited reporting purposes only.

Attribution of the AE:

Definite – The AE **is clearly related** to the study intervention.
Probable – The AE **is likely related** to the study intervention.
Possible – The AE **may be related** to the study intervention.
Unlikely – The AE **is doubtfully related** to the study intervention.
Unrelated – The AE **is clearly NOT related** to the study intervention.

7.3 DSMC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All Adverse Events that occur during protocol intervention and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization≥24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER. All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

7.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

8. Data Management

Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Enrollment Form	Database
Survival Form	Database
Off Treatment Form	Database
Off Study Form	Database
Withdrawal of Consent	Database
Post-Operative Data Collection Form	Database
Adverse Events Log	WISER/OnCore

References

1. Jonczyk MM, Jean J, Graham R, Chatterjee A. Surgical trends in breast cancer: a rise in novel operative treatment options over a 12 year analysis. *Breast Cancer Res Treat*. 2019;173(2):267-274. doi:10.1007/s10549-018-5018-1
2. USCS Data Visualizations. Accessed January 2, 2021. https://gis.cdc.gov/grasp/USCS/DataViz.html
3. 2019 Plastic Surgery Statistics Report. *Plast Surg*. Published online 2019:25.
4. Dassoulas KR, Wang J, Thuman J, et al. Reducing Infection Rates in Implant-Based Breast Reconstruction: Impact of an Evidence-based Protocol. *Ann Plast Surg*. 2018;80(5):493-499. doi:10.1097/SAP.0000000000001407
5. Sharif-Askary B, Vernon R, Broadwater G, Lane W O, Pomann G -M, Hollenbeck ST. Subjective and objective evaluation of breast temperature following post-mastectomy reconstruction. *Breast J*. 2020;26(3):571-573. doi:https://doi.org/10.1111/tbj.13599
6. Sessler DI. Complications and Treatment of Mild Hypothermia. 2001;95(2):13.
7. Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. *The Lancet*. 2001;358(9285):876-880. doi:10.1016/S0140-6736(01)06071-8
8. Kurz A. Perioperative Normothermia to Reduce the Incidence of Surgical-Wound Infection and Shorten Hospitalization. *N Engl J Med*. Published online 1996:7.
9. Sessler DI. Temperature Monitoring and Perioperative Thermoregulation. *Anesthesiology*. 2008;109(2):318-338. doi:10.1097/ALN.0b013e31817f6d76
10. Kankam HKN, Mehta S, Jain A. Thermal Preconditioning for Surgery: A Systematic Review. *J Plast Reconstr Aesthet Surg*. 2020;73(9):1645-1664. doi:10.1016/j.bjps.2020.05.025
11. Ulger H, Erdogan N, Kumanlioglu S, Unur E. Effect of age, breast size, menopausal and hormonal status on mammographic skin thickness. *Skin Res Technol*. 2003;9(3):284-289. doi:https://doi.org/10.1034/j.1600-0846.2003.00027.x
12. Larson DL, Basir Z, Bruce T. Is Oncologic Safety Compatible with a Predictably Viable Mastectomy Skin Flap? *Plast Reconstr Surg*. 2011;127(1):27-33. doi:10.1097/PRS.0b013e3181f9589a
13. Muntean MV, Ardelean F, Strilciuc S, Pestean C, Georgescu AV, Muntean V. Flap warming improves intraoperative indocyanine green angiography (ICGA) assessment of perfusion. An experimental study. *J Plast Reconstr Aesthet Surg*. 2019;72(7):1150-1156. doi:10.1016/j.bjps.2019.03.014
14. Mehta S, Cro SC, Coomber B, Rolph R, Cornelius V, Farhadi J. A randomised controlled feasibility trial to evaluate local heat preconditioning on wound healing after reconstructive breast surgery: the preHEAT trial. *Pilot Feasibility Stud*. 2019;5. doi:10.1186/s40814-019-0392-y
15. Mehta S, Rolph R, Cornelius V, Harder Y, Farhadi J. Local heat preconditioning in skin sparing mastectomy: A pilot study. *J Plast Reconstr Aesthet Surg*. 2013;66(12):1676-1682. doi:10.1016/j.bjps.2013.07.034
16. Braverman IM. The Cutaneous Microcirculation. *J Investig Dermatol Symp Proc*. 2000;5(1):3-9. doi:10.1046/j.1087-0024.2000.00010.x

The following Appendices are required for all WFBCCC cancer treatment protocols.

Add additional appendices as needed.

***ALL** data collection forms must be included as protocol appendices at the time the protocol is submitted to the WFBCCC Protocol Review Committee (PRC) for review.*

Appendix A – Eligibility Checklist

IRB Protocol No.	**WFBCCC Protocol No.**
Study Title: Mastectomy Flap Temperature and Clinical Implications	
Principal Investigator: Adam Katz, MD and Cassandra Driscoll, MD, MPH	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Scheduled for unilateral or bilateral mastectomy with implant based breast reconstruction within the Wake Forest Baptist Health System	☐	☐	
Aged 18 or older	☐	☐	
Ability to understand an IRB-approved informed consent document (either directly or via a legally authorized representative).	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Those who are male	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B-Registration Form

☐ NC002 – WF Main Campus

☐ NC145 – High Point – Hayworth Cancer Center

☐ NC272 – Mount Airy

☐ NC295 – Wilkes

☐ NC273 – Elkin

☐ NC274 – Lexington

☐ NC275 – Clemmons

☐ NC

Registration Date: ___ ___ / ___ ___ / ___ ___

Registered By: _____

Protocol Number _____

Treating MD Name: _____

Date Consent Signed:

(Consent must be signed prior to registration) ___ ___ / ___ ___ / ___ ___

On Arm Date: ___ ___ / ___ ___ / ___ ___

Treatment Assignment/Arm: _____

Wiser Sequence No: _____

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___

DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

Method of Payment: (Private; Medicare; Medicare + Private; Medicaid; Medicaid + Medicare; Military; Veteran Support; Self-Pay; None; Unknown; Other,

Specify)_____

ZIPCODE: ___ ___ ___ ___ ___

Disease Site:_____

Example:C67.9 - Bladder, unspecified

Histology: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___ ☐ Actual ☐ Approximate

INDUSTRY PID:

GROUP PID: (Alliance, ABTC, SWOG, ETC.)

STEP NUMBER: (Alliance, SWOG, ETC.)

ASSIGNED ARM:

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered or e-mailed to the registrar. Registration email: registra@wakehealth.edu.
Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.
Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu, respectively.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?

☐ **Yes** ☐ **No**

Was a discrepancy found? ☐ **Yes** ☐ **No**

If yes, please provide what is currently indicated in the EMR:

Ethnicity: _____ Race: _____

Additional comments:

_____

_____

_____

_____

Appendix D Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP Date: 02/11/2021

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a WFBCCC Investigator Initiated interventional trial if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where all patients are enrolled from one of the WFBCCC sites. These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.

There are three types of trials that are included in this category:

a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization > 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information

into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?
During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?
Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).

2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.

3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.

4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.

5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
   i. DSMC clinician name, date/time contacted and comments
   ii. Date of last dose before the event
   iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification *This is required in order for the email notification to be sent*
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE .
14. Enter Date Notified DSMC -- *This is required for the email notification to be sent*
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the STRC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Glenn Lesser, MD – Hematology Oncology 6-9527 / 6-7972 / Pager 336-806-8397
Mercedes Porosnicu, MD-- Hematology Oncology 6-7980 / 6-0230 / Pager 336-806-9150
Ryan Hughes, MD – Radiation Oncology 3-3600 / Pager 336-806-9865
Michael Goodman, MD -- Hematology Oncology 6-7970 / Pager 336-806-7283
Daniel Reed, MD -- Hematology Oncology 3-3841 / Pager 336-806-0637
Mary Beth Seegars, MD -- Hematology Oncology 6-4815 / Pager 336-806-9948

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

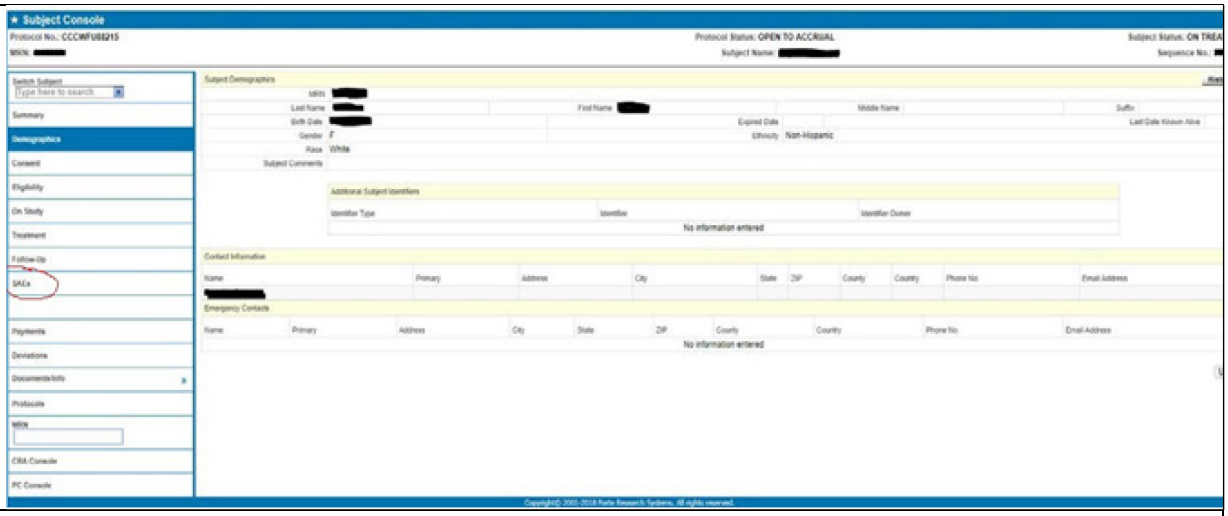
DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment shouldbe considered.

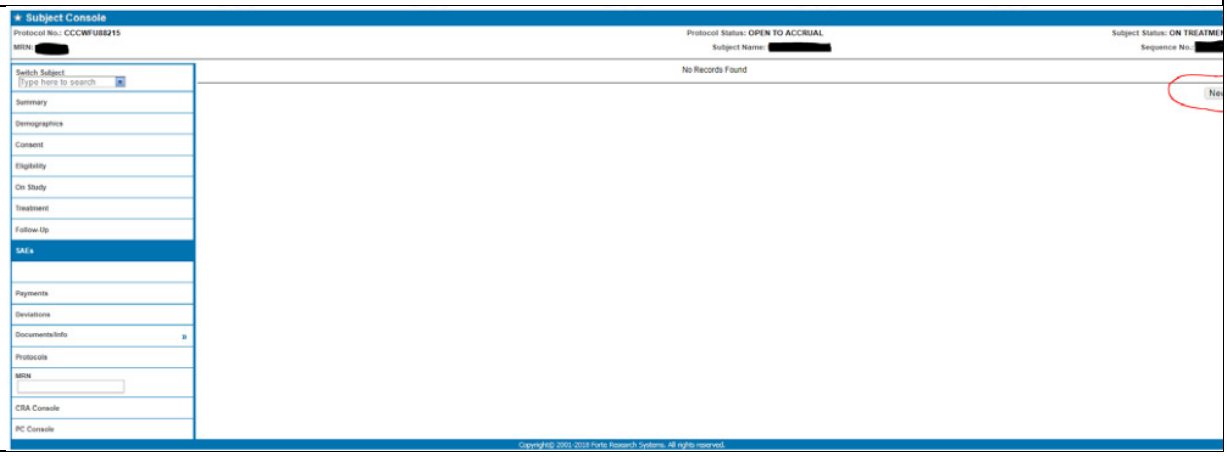
AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

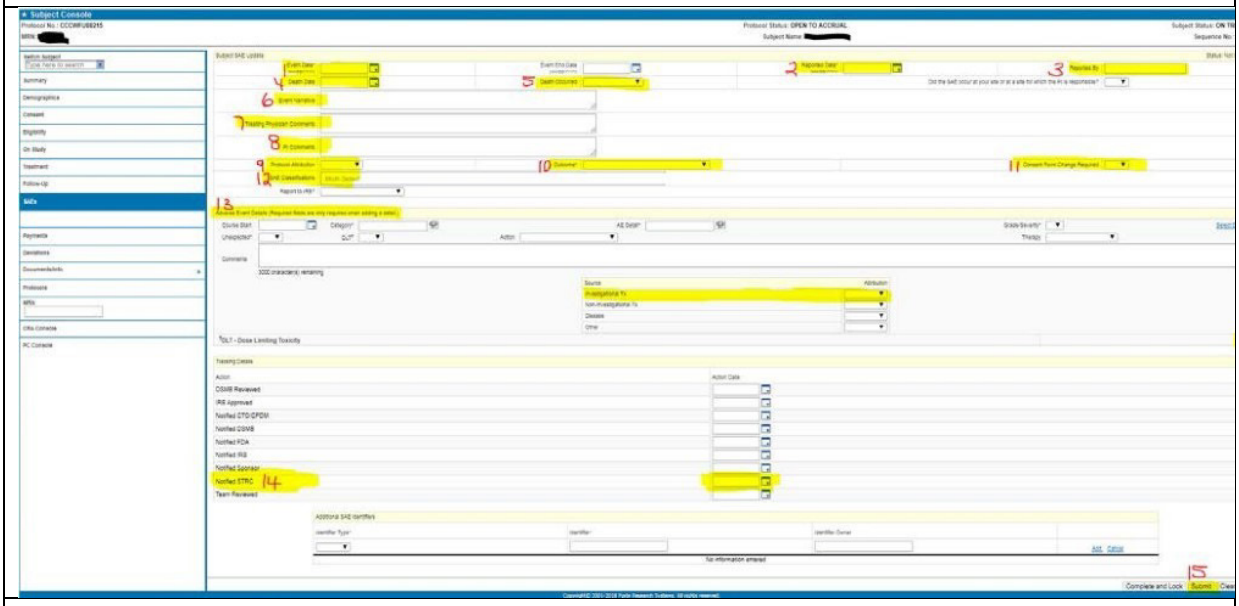
Screen Shot 1:



Screen Shot 2



Screen Shot 3:



Screen Shot 4: