TITLE: Randomized Controlled Trial of Repeat vs. Single Quadratus Lumborum Block to Reduce Opioid Prescriptions After Open Pancreatectomy ("RESQU-BLOCK" Trial)

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Table of Contents

1.0 Objectives

The **primary aim** of this proposal is to use a **phase II randomized controlled trial** to compare the **intervention of a second regional anesthetic block (QL block) versus usual care** (single intraoperative QL block) to **increase the proportion of opioid-free pancreatic cancer survivors** at discharge after potentially curative surgery. The primary outcome measure will be the proportion of patients in each arm who are opioid-free at discharge and thus not requiring any opioids on their discharge prescription. **Both arms will include a standardized non-narcotic bundle** for pain control supplementation during hospital stay and upon discharge and previously published enhanced surgical recovery protocols, based on pancreatic leak risk.

PICO: In patients undergoing open pancreatectomy using general anesthesia with regional pain block (QL block with 72-hr liposomal bupivacaine) [**Patients**], can the placement of a 2nd QL block (on postoperative day 4) [**Intervention**] more effectively wean patients off opioids during the inpatient stay vs. usual care of QL block (both arms with low-dose IV-PCA with non-narcotic bundle) [**Control**]. The primary outcome measure will be the proportion of patients able to be opioid free on discharge prescriptions [**Outcome**].

Outcome Measures:

Primary:

- **Proportion of patients** totally free of opioids on discharge, requiring no opioid prescription.

Secondary:

- **Hospital Measures**
  - Total oral morphine equivalents (OME) mg – which arm is lower and what effect size difference
  - Cost [hospital charges x cost/charge ratio] and cost-benefit analysis
  - Patient Reported Outcomes for gastrointestinal surgery– MD Anderson Symptom Inventory (MDASI-GI) for Patient-Reported Outcomes
- **Discharge Measures**
  - Actual initial discharge pain prescription dosage/size [CDC recommendation is <200mg after surgery]
  - % patients with initial discharge Rx dosage/size total OME <200mg
  - % patients using opioids on POD 30
  - MDASI-GI in clinic visits
  - % pts using opioids at POD 90
  - Total OME for first 30 days and first 90 days [inpatient + outpatient]
  - 6-mo and 1-yr follow-up – pts and family free of opioid use

2.0 Rationale

There is increasing evidence that an elective surgical event is often a patient's initial and greatest exposure to opioids.[1-3] In survivors of cancer surgery, persistent opioid use can be predicted by the dispensed amount of a patient's initial outpatient prescription at surgical discharge.[1,4,5] Furthermore, national prescribing pattern data have shown that the initial outpatient prescription of *oral morphine equivalents (OME)* can be predicted by opioid utilization during the last 24hrs in the hospital.[6,7] A tangible contribution from the surgical community would be the active implementation of a protocol to eliminate or reduce outpatient opioid dissemination in a

greater proportion of cancer survivors after oncologic surgery. In this context, we have implemented regional anesthetic techniques including ultrasound-guided four-point *bilateral quadratus lumborum (QL) block using 72-hr liposomal bupivacaine.* Despite the success of reducing our median length of stay from 10 days to 6 days with enhanced recovery protocols in 2016-17, only 5% of our patients were discharged without opioids after review of 158 consecutive pancreatectomy patients. Median initial outpatient prescription OME was 316mg, far above the 200mg OME recommended by the Centers for Disease Control.[8] We thus see an opportunity to improve rapid postoperative opioid weaning to increase the proportion of opioid-free patients at surgical discharge. We hypothesize that a second, repeat QL block on postoperative day 4 will bridge the gap between the initial intraoperative QL block and ambulatory status, and increase the proportion of cancer survivors without postoperative outpatient opioid prescriptions. **Rescue blocks are currently used on an as-needed basis** only when the first block is insufficient or if the clinical team decides that the opioid use is subjectively too much**. We have not routinely used a 2nd block, because opioid-free discharge has never previously been a goal.** Our new goal is to **reduce dissemination of opioids into the community and reduce the risk of persistent opioid use among survivors.**

"Enhanced recovery after surgery," or ERAS, is no longer a novel idea. However, its benefits are beginning to be seen beyond the early metrics of hospital stay and activities of daily living. Downstream benefits have included reduced complications, less readmissions (despite earlier discharges), less hospital resource consumption (cost), and improved postoperative quality of life. With the opioid epidemic increasingly discussed in both medical and lay literature, we are seeking to modify our enhanced recovery program in abdominal cancer surgery to reduce opioid exposure in the hospital. Medical literature has shown that oftentimes the first exposure or greatest exposure to opioids comes from an elective surgical event. Persistent opioid use (past 1yr) can be predicted by the size of a patient's initial outpatient prescription **oral morphine equivalents (OME)**. And the **initial outpatient prescription OME can be predicted by the amount of opioids used in the last 24hrs of hospitalization**.

We recently analyzed 158 consecutive pancreatectomy patients' opioid use by converting units into OME using an automatically generated download from our electronic health record. In our analysis, we found that intravenous patient-controlled anesthesia (IV-PCA) represented the largest contributor to total inpatient OME, even when universally paired with an ultrasound-guided regional anesthetic block with 72-hr liposomal bupivacaine**.** Median total OME (from all sources of pain control) for patients with IV-PCA was 525mg (range 28-4,362mg). Median OME contribution from IV-PCA alone was 373mg. **Only 5% of patients were discharged without opioids**. Median initial outpatient prescription OME was 316mg, far above the 200mg OME recommended by the CDC. We thus see an **opportunity to reduce opioid exposure** to increase the **proportion of opioid-free patients at discharge**. We are already embarking in improving our "usual care" enhanced surgical recovery bundle by using standardized non-narcotics and reducing initial IV-PCA settings.

HYPOTHESIS

- We hypothesize that a **second, repeat QL block on postoperative day 4** will bridge the gap between the initial intraoperative QL block and ambulatory status, facilitating a rapid opioid wean and **thus increase the proportion of cancer survivors without postoperative outpatient opioid prescriptions.** Ultimately, this should reduce dissemination of opioids into the community and reduce the risk of persistent opioid use in survivors.

3.0 Eligibility of Subjects

Inclusion:

- patients ≥ 18 years of age undergoing elective open pancreatic resection for potentially curative intent (pancreaticoduodenectomy or distal pancreatectomy) who would otherwise be treated with QL block + IV-PCA converted to oral pain meds [non-narcotic bundle + opioid pain pill].

Exclusion:

- Patients with current or past substance [drug or alcohol] abuse disorder
- Laparoscopic or minimally invasive surgery

4.0 Research Plan and Methods

This is a **single-center phase II open-label randomized controlled trial** to assess the effect of an additional QL block on POD4 in patients undergoing pancreatic surgery with potentially curative intent. The primary endpoint is the proportion of patients who are **opioid-free on the discharge date**. Patients will be randomized with 1:1 ratio to receive either QL in OR + non-narc bundle +/- low-dose IV-PCA (control arm) or QL in OR and QL on POD4 AM + non-narc bundle +/- low-dose IV-PCA (experimental arm). The **allocation will be concealed until postoperative day 1** so that clinicians at the time of surgical consent will not be able to predict to which pathway the next enrollee will be assigned. Patients will be stratified based on pathway allocation (Green vs. Orange vs. Blue) and preoperative average daily OME use in the past 7 days (>5mg vs. ≤5mg OME).

Our **3 colored pathways are based on clinical predictors of pancreatic leak risk and thus median length of stay**. The median length of stay for Green (low-risk pancreatoduodenectomy), Orange (high-risk pancreatoduodenectomy), and Blue (distal pancreatectomy) patients is 6, 8, and 5 days, respectively. The length of stay affects the weaning, in that longer stays allow more time to wean off inpatient opioid use.

Method of Group Assignment and Randomization

Sequence Generation: Redcap will be used for 1:1 allocation with stratification for **postoperative pathway (Green, Orange, or Blue) which is determined preoperatively based on risk of pancreatic leak** and preoperative average daily OME use in the past 7 days (>5mg vs. ≤5mg OME).

Allocation Concealment and Mechanism: Allocation will be concealed at the time of enrollment from patients, providers, and researchers.

Implementation: Acute pain team, surgeons, advanced practice providers, fellows, and nurses will perform interventions and assessments per standard of care.

Blinding: All clinicians and patients will be **blinded from the allocation before surgery, intraoperatively, and until POD1**. The only difference in intervention will be the 2nd QL block which cannot be blinded.

Intervention Strategy:

On postoperative day 4 [at least 96hrs from initial QL on postoperative day "0", which is the day of surgery, per FDA guidelines], patients will undergo a 2nd QL procedure in the regular hospital room by the Acute Pain Service attending anesthesiologist using ultrasound guidance, which is usual routine method. The intent will be to do the 2nd QL.

This will be a **Type I QL block,** which allows an anterior approach to the correct fascial layers. Using sterile technique, the attending anesthesiologist will guide the needle through the appropriate skin, subcutaneous, and muscle layers to find the right fascial plane **using ultrasound localization**. The risk of complications is virtually nil, because most hospital subcutaneous and intramuscular shots which are done blindly or by "landmark," the QL block will be done by exact ultrasound guidance. **This block will only be done by Acute Pain Service certified attendings**. We are not studying this block's mechanism or the drug's mechanism – both of which are well documented in 1000's of patients. **This RCT focuses on the novel timing of using this regional block to augment the opioid weaning process.**

Patients or providers may choose to forego the option if patients are already opioid-free or nearly opioid-free. If the patient is discharged before POD4, there will not be any 2nd injection. The **usual measures of non-narcotic bundle** [including acetaminophen, NSAIDs, muscle relaxers, and Lidocaine-secreting patches] and conversion from IV pain meds to oral pains will be done to reduce total opioid exposure and use.

The 2nd block is a "Rescue Block" which we currently utilized on the floor for patients with pain control that is not making the anticipated progress on postoperative day 4, and if we want to avoid opioids due to traditional issues like ileus, somnolence, and nausea. Thus, in terms of hospital billing, this is still within the realm of usual care. It is not experimental therapy.

There will be no sham procedure in the control arm. In other words, there will not be any subcutaneous injection of placebo drug in patients in the control arm, since this is a study of treatment sequencing rather than one focused on the drug itself. A sham procedure would be required if we were using an experimental drug in the intervention arm, but the analgesic effect of bupivacaine is well-proven already. We chose against a sham needle injection since the primary aim of this study focused on treatment sequencing with primary endpoint being opioid-free discharge. The "treatment" herein is the bundle of standardized non-narcotics and the clinical care that is typically given for weaning pain medications through an inpatient stay. The only difference between the 2 arms is that the "intervention" arm has the option (patient may refuse if they are already off opioids) for the rescue block while the "comparison/control" arm has to use usual measures to continue weaning opioids.

Pain measurement: Pain scores will be measured using usual care – visual analog scale by hospital inpatient nurses. They ask the patient every 4hrs on a scale 0-10, and this is documented in the EHR. Nurses then offer patients with symptomatic scores additional oral or IV pain meds as appropriate based on usual clinical care (IV if not eating or severe breakthrough pain) and oral if eating and pain is not urgent.

- **Liposomal bupivacaine – 72-hr action**
    - No repeat in 96 hrs per drug label
    - Rarely completely enough for pain control – often needs low-dose IV-PCA as well, but can reduce total opioid use if an opioid-sparing bundle is standardly used, which we will do (both arms get the same non-narcotic bundle in hospital and upon discharge).

- **Dosage instructions in Figure 3 below.** The Operating Room pharmacy has calculated the appropriate max dose of long-acting and short-acting bupivacaine which can be safely mixed. There are laminated placards in every operating room, and most nurses know the mixture by memory. Certainly the Acute Pain Service attendings do as well since they have performed 1000's of these injections in the past few years.
- **Liposomal bupivacaine has become our standard of care for open surgery.** We use this in 90% of our pancreas patients, while the other 10% get epidurals. There is extensive experience using liposomal bupivacaine for regional blocks. This RCT does not focus on the use of the block per se (since it is routine care), but rather the timing of it.

Comparison Strategy:

The control arm patients will have usual care with just the single QL using ultrasound guidance placed in the OR. When the liposomal bupivicaine wears off, **there will be no second QL**. The **usual measures of non-narcotic bundle** [including acetaminophen, NSAIDs, muscle relaxers, and Lidocaine-secreting patches] and conversion from IV pain meds to oral pains will be done to reduce total opioid exposure and use. Due to risk of harm from injection of placebo, there will not be any sham procedure

Decision on Discharge Opioid Prescription

To avoid bias in one arm or the other, all discharge prescriptions will standardized. Both arms will get standard non-narcotic bundles of acetaminophen 650mg q6hrs, celecoxib 100mg q12hrs, and methocarbamol 250-500mg q8hrs. Slight dose variations can be allowed here based on pharmacy availability (e.g. recent national shortage of methocarbamol 500mg pills). To standardize the opioids, we will use a multiplier of 5 days x the last-24hrs opioid pill count. This can found easily in the electronic health record. We chose 5 days because the CDC recommends 7 days max prescription and less than 200mg OME. All patients have clinic appointments within one week of discharge and have phone numbers to call if their multimodal pain management plan is insufficient. The chance of this is very low considering these patients are on the same plan on discharge as they have been in the last 24hrs in the hospital. The multiplier of objective opioid pain pill use will be more useful than the subjective pain score which varies from patient to patient in their interpretation of that "smiley-face" Likert scale.

Interim Analyses:

One interim analysis will be performed when half of the patients (N=53) have been randomized and received treatment. The trial will be stopped due to futility if the p-value is >0.774 for the primary endpoint.

Anticipated Results:

Participant Flow Diagram: see Figure 1

Recruitment

All patients meeting inclusion criteria above will be recruited from clinic either during the consultation meeting or during the preoperative meeting. Prior to these meetings, the patients may be sent a letter through MyChart (Appendix E) requesting permission to seek financial clearance in advance, to avoid delays should the patient agree to participate in the study.

Generalizability

The chosen regional block is a well-documented procedure in the anesthesia literature. The drug used in the block is universally available for other types of block. The non-narcotic

bundle consists of generic drugs with minimal costs and are all well within usual care guidelines. The postoperative care pathways are published and reproducible.

Potential Harms/Adverse Events:

- Because regional blocks with liposomal bupivacaine are standard of care and have been performed in 1000's of MD Anderson Cancer Center patients, there almost no clinically relevant adverse events that we anticipate besides the "trouble" of collecting the equipment, gathering the Acute Pain Service, and asking the patient to lie flat in bed for 30min on POD4. This is an extra procedure at bedside on POD4
- There could be pain and anticipatory anxiety for the bedside procedure
- Hematoma from needle sticks are possible but almost never seen
- There is the cost of the procedure which is a "rescue block," which we have used before for failed 1st time blocks. **We have just never used it as a supplemental block to wean patients completely off opioids, because being opioid-free has never been a priority.** The reality is that it is "easier" to just order oral opioids on POD4 and beyond rather than going to the "trouble" of doing a bedside procedure on POD4 to get a patient potentially opioid-free.
- Unblinded providers affecting discharge OME in one arm over another. We will minimize this using 2 methods to protect patients:
    - Standardized IV-PCA settings will be used starting in the recovery room immediately out of the operating room. Unless there is an allergy, we will use our standard medication, dilaudid 0.1mg IV q 10min as needed, with no basal dose. This can be adjusted based on clinical needs. This will be weaned off when the patient starts solid food diet.
    - Patients' daily pain scores (checked by nurses q4hr) will be used to ensure that adequate pain control prescribed before discharge. There is no "threshold" score that will be used since one patient's "4" is different than another patient's "4," but the trend will be useful to ensure patients are not being ignored. More importantly, all patients will be judged by their activities of daily living on the last 24hrs to ensure pain control is adequate.
    - **The number of opioid pills will be formulaic to avoid bias by clinicians or patients in one arm or the other - we will take the last 24hrs of inpatient opioid pills used and <u>multiply by a factor of 5 days</u> to make this number standardized between the 2 arms.**
    - **Both arms get the same non-narcotic pain management bundle for inpatient and discharge.**
- **Prospective AE Records**
    - Inpatient advanced practice providers (nurse practitioner or physician assistant) will document complications daily prospectively
    - **Hospitalization, 30-day, and 90-day complications prospectively recorded** into our Pancreas Surgery Database RCR01-112 systematically on a weekly basis with faculty attendance
    - **We record all complications for 90 days after all operations using our faculty-led weekly review. Therefore we plan to ask for DSMB waiver since we are not doing any experimental procedure or using any new drug.**
- **Safety Review**
    - If the analysis of the first 20 patients yields complication rates from the intervention arm above the *pre-determined acceptable level*, the study will be terminated. This level is at least 25% of patients requiring deviation from their usual pathway and anticipated stay.

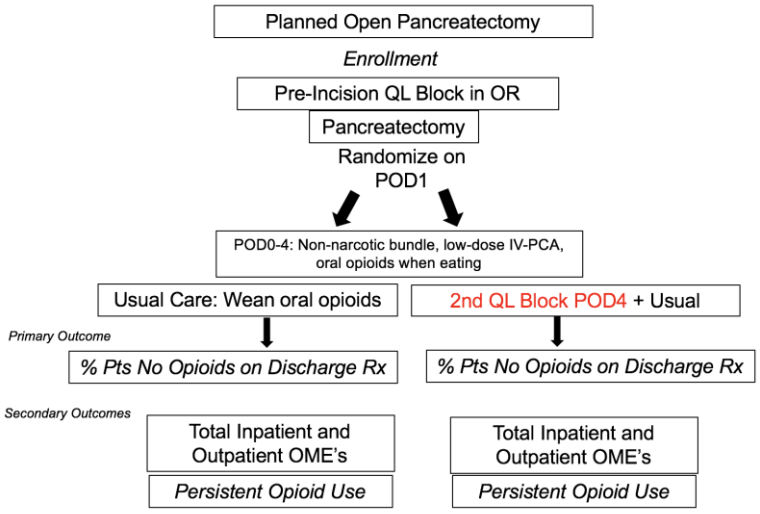


Figure 2. Study intervention timeline

	Pre-Op Days	Inpatient Postop Day										Outpatient Month [a, b]			
Time	-30 to 0	PACU "0"	1	2	3	4	5	6	7	8	DC	1	3	6	12
Oral Morphine Equivalents	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MDASI-GI	X					X					X[c]	X		X	X
Pain Score	X	X	X	X	X	X	X	X	X	X	X				
Hospital Cost											X				
Adjuvant Therapy [if needed]												X		X	X
Informed Consent	X														

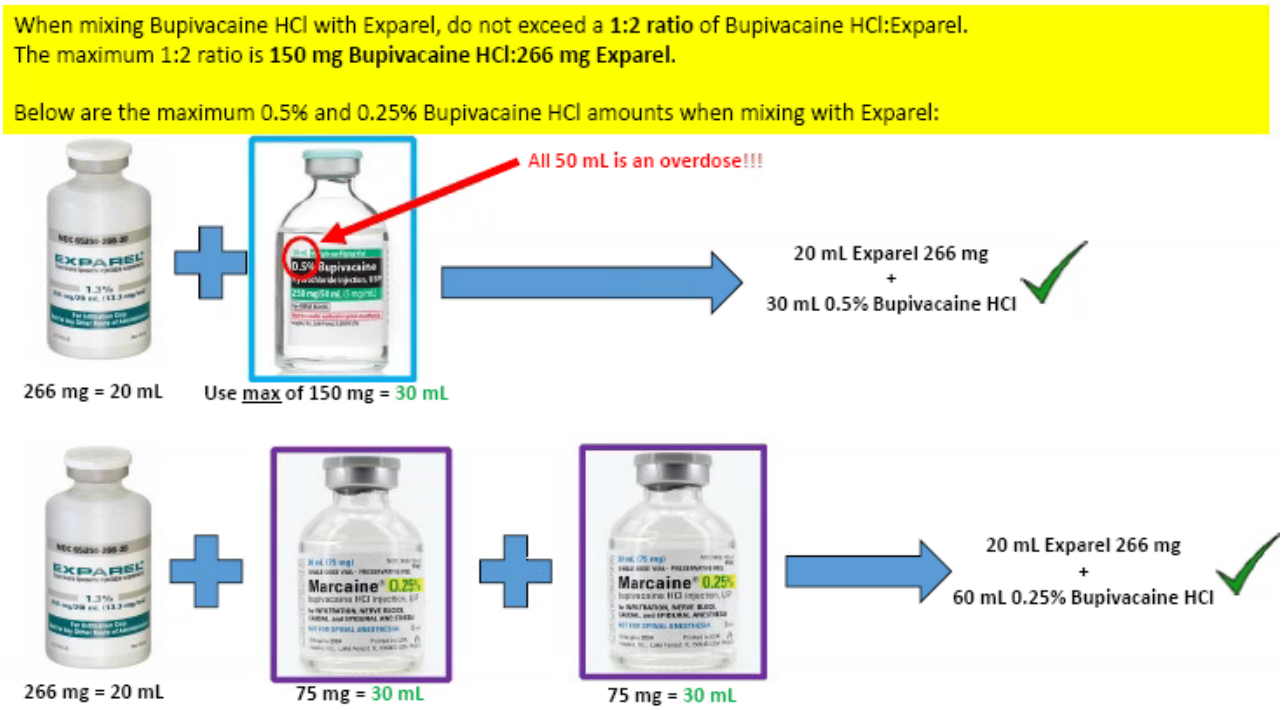
Median Length of Stay is 5 days for Blue Pathway, 6 for Green, and 7 for Orange Pathways.

Day of surgery is called postoperative day "0" and the 1st day after surgery is called postop day 1. This is different than medical terminology in which the "count" of hospital days starts at "1," not "0" as with surgery.

a. +/- 1 week for outpatient follow up.
b. Survey may be administered via phone, email, or in clinic.

c. Survey may be administered from day of discharge to the first post-OP visit via phone, email, or in clinic.

Figure 3. Liposomal bupivacaine mixture recommendations from OR Pharmacy [approved 2 years ago].



5.0 Statistics and Justification of Sample Size

For the primary analysis, we will perform Chi-squared test to compare the proportion of patients who are opioid-free on the discharge date between the two arms. As a secondary analysis, we will also perform the Cochran–Mantel–Haenszel test to take into account the stratification factors. In addition, stratified logistic regression analysis will be carried out to assess the difference between the two arms after adjusting for the stratification factors and other patient characteristics at baseline. Similar analyses will be performed for other binary secondary outcomes, such as discharge Rx dosage/size total OME <200mg (yes vs. no), opioids usage on postoperative days 30, 90, 180, and 365 (yes vs. no), etc. Two sample t-test or Wilcoxon rank-sum test will be used to compare continuous secondary outcomes such as total inpatient OME, cost, QOL scores, pain prescription dosage at first discharge, etc. Other statistical analyses may be performed as appropriate.

Based on historical data, we anticipate that 5% patients in the control arm will be opioid-free in their discharge prescriptions, while with the additional TAP block in the experimental arm, it will increase the proportion to 25%. Under this assumption, the study will require 106 **patients (53 per arm)** in order to have 84.5% power to detect such a 20% difference, using two-sided Chi-squared test and with 5% significance level. East6.3 was used for the sample size calculation. Assuming a liberal 10% dropout rate, a total of 118 patients will be enrolled from our single institution. Based

on our historical operation volume of 120 patients per year, we anticipate the ability to complete enrollment within 1 year of opening the protocol. One interim analysis will be performed when half of the patients (N=53) have been randomized and received treatment. The trial will be stopped due to futility if the p-value is >0.774.

- Power and significance: 84.5% power (β=0.155) and α=0.05 (two-sided)
- Baseline estimate of control group with no opioids on discharge day: **5%**
- Estimate of experimental: **25%**
- Sample size per arm: 53 pts
- Assume 10% dropout: 59 per arm
    - [1 year to complete enrollment]

In order to enroll the total 118 patients, we will screen up to 140 patients in order to account for screen failures and those who are ineligible due to aborted surgeries.

6.0 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.0 Data Confidentiality:

Data will only be available to the PI and people directly involved with the collection and analysis of data related to this project. IRB approval will be obtained for any exchange of data outside of MD Anderson. All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed

8.0 References

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9.0 Data Monitoring

This protocol will be monitored by the MD Anderson DSMB.