Thomas Jefferson University

THOMAS JEFFERSON UNIVERSITY
Kimmel Cancer Center

A prospective randomized controlled trial evaluating an accelerated 5 day pathway for discharge following pancreaticoduodenectomy (PD): Whipple Accelerated Recovery Pathway (WARP trial)

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Harish Lavu
3/23/17

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List of Abbreviations

Insert the abbreviation and definition for all abbreviations used throughout protocol.

Study Summary

Title	A prospective randomized controlled trial evaluating an accelerated 5 day pathway for discharge following pancreaticoduodenectomy (PD): Whipple Accelerated Recovery Pathway (WARP) trial
Short Title	Whipple Accelerated Recovery Pathway (WARP) trial
Protocol Number	
Phase	N/a
Methodology/Study Design	Randomized, controlled
Study Duration	3 years
Study Center(s)	Single-center
Objectives	The use of an accelerated pathway will result in a shorter postoperative hospital length of stay for patients undergoing PD without an increase in perioperative complications or readmission rates.
Number of Subjects	138
Diagnosis and Main Inclusion Criteria	Pancreatic cancer Inclusion: undergoing pancreaticoduodenectomy, firm gland texture
Study Therapy, Dose, Route, Regimen	N/A Study evaluating postoperative pathway with intensified physical therapy
Duration of administration and follow-up	N/A. Anticipated hospital stay 5-7 days, follow-up per routine postoperative follow up
Reference therapy	Comparison to be made to standard 7-day discharge pathway
Statistical Methodology	Two-sided alpha 0.05, power 80% to detect a increase in the proportion of patients discharged on POD 5 from 10% to 30%; 69 patients needed in each arm (138 total patients).
Schema	Pancreatic mass → eligible for resection → consent obtained → operative resection → randomization to 5 or 7 day discharge pathway → prospective collection of complications, length of stay, and cost data → phone calls to patients on first and second days after hospital discharge → standard routine outpatient follow-up afterwards.

1.0 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Specific Aims and Hypothesis

Hypothesis: The use of an accelerated pathway will result in a shorter postoperative hospital length of stay for patients undergoing PD without an increase in perioperative complications or readmission rates.

Primary endpoint: Post-operative length of stay (proportion of patients discharged by POD 5)

Secondary endpoints: Post-operative median length of stay, cost, readmission rate, post-operative complications (DGE, anastomotic leaks, intra-abdominal abscesses, wound infection, UTI, respiratory compromise, renal failure, etc.)

1.2 Background and Rationale

Standardization of post-operative care pathways has resulted in improved perioperative outcomes following complex abdominal operations. This has resulted in a shorter length of stay for many patients.

In pancreaticoduodenectomy specifically, the implementation of a post-operative pathway here at Jefferson has reduced the median length of stay to seven days and demonstrated that a fair proportion of patients (10%) leave the hospital in as early as five days. There are many reasons to encourage a shorter length of stay for these complex patients including: potential benefit to early mobilization and return to the home setting, decrease in hospital-acquired infectious complications, and of increasing importance in the modern setting, potential cost savings.

1.3 Study Therapy

1. Outpatient office: consent is obtained at the time of procedural consent during preoperative visit
2. Patients get standard preoperative, anesthetic, and operative protocols.
3. Randomization occurs at the end of the case when inclusion/exclusion criteria met.
4. The control arm follows the standard 7 day pathway
5. Care for the intervention arm is focused on seven specific interventions:
    a. All patients are volume restricted in the perioperative period.
    b. More rapidly leaving the ICU setting: Transfer from the ICU to floor directly following review of AM labs on POD 1

c. More restful night sleep, 8 hour undisturbed period for patients recovering without apparent complication: routine lab draws starting POD 2 done at 6 am (rather than 1 am), midnight nursing rounds for vital signs are adjusted to 10 pm.
d. Early mobilization and enhanced physical therapy: formalized physical therapy protocol emphasizing early, frequent ambulation and mandated evaluation in the gym on POD 4 and 5. Physical therapy BID beginning POD 3 (may need adjustment to POD 4 or 5 pending PT staffing resource review)
e. Dietary modification: anticipated discharge with patients on 2/3rds liquid diet with dietary guidelines provided
f. Increased, and standardized, phone contact by nurse practitioner on first two days following hospital discharge.

6. Both groups: MO/RT referrals made on POD4, routine post-operative drain amylase studies POD 3, objective PT score for all patients on POD 5 (based on % of baseline timed get up and go), Attending survey to be completed POD 5 documenting readiness for discharge and rationale, discharge is at the discretion of the attending surgeon, routine drain amylase prior to removal to facilitate early decisions on drain removal v. anticipated discharge with drain in place.

1.4 Preclinical Data

In an informal review of our perioperative outcomes, we've found that nearly 10% of our patients at present leave the hospital five days following pancreaticoduodenectomy.

1.5 Clinical Data to Date

In an informal review of our perioperative outcomes, we've found that nearly 10% of our patients at present leave the hospital five days following pancreaticoduodenectomy.

1.6 Dose Rationale and Risk/Benefits

The major risks for this research are the development of postoperative complications in the outpatient setting, where identification of these complications may be delayed. The risk of fall due to early mobilization with physical therapy, and the potential for dehydration if patients are not able to tolerate adequate oral intake to maintain hydration at home following discharge. Specific measures to minimize these risks are detailed in the next question. Additional risks include violation of loss of confidentiality or violations in protecting personal health information.

The risk of a delayed diagnosis of postoperative complications will be mitigated with increased outpatient communication including daily phone calls and liberalized use of visiting nursing services and outpatient physical therapy. The risk of falls due to early mobilization will be mitigated by having physical therapy

and/or occupational therapy staff present at all additional therapy sessions beyond our current 7 day standard. The risk of dehydration will be mitigated by frequent daily phone contact by a highly-qualified nurse practitioner in the postoperative outpatient setting. Standard protocols as detailed above will be in place to protect patient PHI.

Patients in the study will benefit from increased and standardized physical and occupational therapy services in the postoperative setting, potential for improved pain control through the use of multimodal therapy, and increased preoperative and postoperative outpatient support by a highly-qualified service-specific nurse practitioner.

Decreased length of hospital stay and increased support (as detailed above) may prove to reduce the rate of overall complications and will allow patients return home quicker. Additional benefit may come in the form of reduced overall cost of care.

2.0 STUDY OBJECTIVES

Primary endpoint: Post-operative length of stay (proportion of patients discharged by POD 5)

Secondary endpoints: Post-operative median length of stay, cost, readmission rate, post-operative complications (DGE, anastomotic leaks, intra-abdominal abscesses, wound infection, UTI, respiratory compromise, renal failure, etc.)

2.1 Primary Objective:

The use of an accelerated pathway will result in a shorter postoperative hospital length of stay for patients undergoing PD without an increase in perioperative complications or readmission rates.

2.2 Secondary Objective:

We anticipate lower cost, similar readmission rate, similar rate of post-operative complications (DGE, anastomotic leaks, intra-abdominal abscesses, wound infection, UTI, respiratory compromise, renal failure, etc.) in our study group

3.0 STUDY DESIGN

3.1 General Design

Include:

- *Randomized, controlled, non-blinded clinical trial*
- *Expected duration of subject participation: 5-7 days in hospital with study participation until their first postoperative visit*

3.2 Primary Study Endpoints

Primary endpoint: Post-operative length of stay (proportion of patients discharged by POD 5)

3.3 Secondary Study Endpoints

Secondary endpoints: Post-operative median length of stay, cost, readmission rate, post-operative complications (DGE, anastomotic leaks, intra-abdominal abscesses, wound infection, UTI, respiratory compromise, renal failure, etc.)

3.4 Primary Safety Endpoints

Perioperative complications, morbidity, mortality, and hospital readmission will all be tracked

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

Inclusion criteria: Pancreaticoduodenectomy, firm gland texture, subjects able to provide informed consent

4.2 Exclusion Criteria

Exclusion criteria:

- Preoperative factors: CHF, ESRD, COPD, pregnancy, albumin < 3 gm/dL, poor preoperative performance status as defined by: timed get up and go (<15 seconds), patients cannot be homeless or have substance dependence
- Intraoperative factors: EBL > 1 liter, failure to extubate at the conclusion of the case, operative time > 8 hours, need for vascular resection/reconstruction

4.3 Gender/Minority/Pediatric Inclusion for Research

Men, women, and minorities will all be included. There will be no pediatric patients included in this research

4.4 Subject Recruitment and Screening

138 adult patients will be recruited from the outpatient surgical clinics of the Pancreas, Biliary and Related Cancer Center. Investigators (surgeons) will offer enrollment at the time of consent for pancreaticoduodenectomy.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subjects

A subject may withdraw from the study at any time by contacting any of the physician researchers and making their wishes known

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Data will be used for the purposes of the observation portion of the study up to the point of their withdrawal, any subsequent data will not be collected.

5.0 STUDY DRUG/THERAPY

5.1 Description

1. Outpatient office: consent is obtained at the time of procedural consent during preoperative visit
2. Patients get standard preoperative, anesthetic, and operative protocols.
3. Randomization occurs at the end of the case when inclusion/exclusion criteria met.
4. The control arm follows the standard 7 day pathway
5. Care for the intervention arm is focused on seven specific interventions:
    a. All patients are volume restricted in the perioperative period.
    b. More rapidly leaving the ICU setting: Transfer from the ICU to floor directly following review of AM labs on POD 1
    c. More restful night sleep, 8 hour undisturbed period for patients recovering without apparent complication: routine lab draws starting POD 2 done at 6 am (rather than 1 am), midnight nursing rounds for vital signs are adjusted to 10 pm.
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    e. Dietary modification: anticipated discharge with patients on 2/3rds liquid diet with dietary guidelines provided
    f. Increased, and standardized, phone contact by nurse practitioner on first two days following hospital discharge.
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5.2 Treatment Regimen

N/A, plans as described above

5.3 Risks

The major risks for this research are the development of postoperative complications in the outpatient setting, where identification of these complications may be delayed. Other risks to these patients that are not present in our

standard 7 day discharge patient includes the the risk of fall due to early mobilization with physical therapy, and the potential for dehydration if patients are not able to tolerate adequate oral intake to maintain hydration at home following discharge. Specific measures to minimize these risks are detailed in the next question. Additional risks include violation of loss of confidentiality or violations in protecting personal health information.

The risk of a delayed diagnosis of postoperative complications will be mitigated with increased outpatient communication including daily phone calls and liberalized use of visiting nursing services and outpatient physical therapy. The risk of falls due to early mobilization will be mitigated by having physical therapy and/or occupational therapy staff present at all additional therapy sessions beyond our current 7 day standard. The risk of dehydration will be mitigated by frequent daily phone contact by a highly-qualified nurse practitioner in the postoperative outpatient setting. Standard protocols as detailed above will be in place to protect patient PHI.

Patients in the study will benefit from increased and standardized physical and occupational therapy services in the postoperative setting, potential for improved pain control through the use of multimodal therapy, and increased preoperative and postoperative outpatient support by a highly-qualified service-specific nurse practitioner.

Decreased length of hospital stay and increased support (as detailed above) may prove to reduce the rate of overall complications and will allow patients return home quicker. Additional benefit may come in the form of reduced overall cost of care.

5.4 Method for Assigning Subjects to Treatment Groups

Patients will be randomized at the end of their operation by calling a study coordinator who will open envelopes in sequential number with treatment group detailed inside. Treatment group will be randomly sealed in envelopes prior to study initiation.

5.5 Preparation and Administration of Study Drug/Therapy

N/A, interventions as described above

5.6 Subject Compliance Monitoring

Compliance will be monitored during the patient's inpatient hospital stay and by daily phone calls on the first two days out of the hospital and all subsequent follow-up visits.

5.7 Prior and Concomitant Therapy

- N/A

5.9 Blinding of Study Drug

Unblinded study

5.10 Receiving, Storage, Dispensing and Return

6.0 STUDY PROCEDURES

6.1 Study Visit Schedule

Visit 1: If patient deemed surgical candidate, enrollment offered

Visit 2: Hospital stay, details as above. Follow-up thereafter is per post-surgical routine

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

The primary outcome is the proportion of patients discharged on postoperative day 5. Group sample sizes of 71 in group one (standard pathway) and 71 in group two (intervention arm) achieve 80% power to detect a difference between the group proportions of 0.20 (for patients discharged on postoperative day 5). The proportion in group two (intervention arm) is assumed to be 0.10 under the null hypothesis and 0.30 under the alternative hypothesis. The proportion in group one (the control group) is assumed to be 0.10 (the proportion in historical data is approximately 0.09). The test statistic used is the two-sided Fisher's Exact test. Power was calculated via simulation assuming an alpha of 0.05 spent between the interim and final analysis using an O'Brien-Fleming spending function as outlined below. In simulation of 100,000 trials, if the true rate in the intervention group is 0.30, the study stopped early for efficacy 16.2% of the time.

7.2 Statistical Methods

Baseline demographic variables will be summarized by randomization arm using means and standard deviations (for continuous variables) or frequencies and percentages (for categorical variables), as appropriate.

Primary Outcome:
Randomization arms will be compared with respect to the primary outcome, proportion of patients discharged on postoperative day 5 using Fisher's Exact test. One interim analysis for efficacy will be performed when 72 patients have been randomized and completed follow-up for the primary outcome. The study will stop for efficacy if the p-value of the Fisher's exact test is less than 0.00506 at the interim analysis. Assuming the efficacy bound is not met, the null hypothesis will be rejected at the final analysis if the p-value is less than 0.04553.

Secondary outcomes:
Differences among treatment groups with respect to secondary continuous outcomes (post-operative median length of stay, cost) will be assessed using two-sample t-tests or Wilcoxon rank sum tests. Differences in binary outcomes (readmission rate, post-operative complications, delayed gastric emptying, anastomotic leaks, intra-abdominal abscesses, wound infection, urinary tract infection, respiratory compromise, renal failure) will be assessed using Chi-square tests or Fisher's exact test)

Safety:
The primary safety outcome is hospital readmission. We will employ a Bayesian safety monitoring rule to stop the study if $\Pr(\pi_{5day} - \pi_{control} > 0.05) > 0.9$ where π_{5day} is the true rate of hospital readmission under the 5 day protocol and $\pi_{control}$ is the rate under standard of care. The rule means we will stop the study if there is high posterior probability (greater than 90%) that the readmission rate is 5% higher with the 5 day protocol than under standard of care. Over the last 1000 cases, the rate of readmission under standard care is 15%. We assume prior distributions of $\pi_{5day} \square Beta(0.2,0.8)$ and $\pi_{control} \square Beta(15,85)$. That is, we assume the rate in under the 5 day protocol is higher, but with fairly high uncertainty, and we assume 15% under control equivalent to information from 100 subjects. Posterior probabilities will be calculated at the time of the interim efficacy analysis and every 12 patients thereafter. Stopping rules at the interim analysis (36 patients per group) are shown below:

Readmissions in Standard of Care (out of 36)	Stop if Readmissions in 5 day arm are >= (out of 36)
1-2	10
3-5	11
6-8	12
9-12	13

7.3 Subject Population(s) for Analysis

Primary Analysis Population: All randomized patients will be analyzed as randomized in an intention to treat manner. We expect length of stay to be complete for all patients. Any subjects missing length of stay data will be excluded from all analyses. Subjects without data for a particular secondary outcome will be excluded from the analysis of that outcome.

As-treated Population: Supplemental analysis may be considered analyzing patients "as-treated" if it is determined that more than 5% of subjects were not treated as randomized.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious.

A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end

of the study treatment follow-up. Adverse event reporting will continue until 90 days following their operation or the end of their index hospitalization (whichever is longer).

Preexisting Condition

Preexisting conditions that can worsen during the study period will only be reported if they are related to the study intervention.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to the interventions in this study. The investigator should notify the IRB of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to the study interventions.

Abnormal Laboratory Values

A clinical laboratory abnormality related to the study interventions should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded if related to the study interventions.

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study interventions should be recorded and reported immediately.

8.4 Stopping Rules

Stopping rules for efficacy and safety are outlined in the statistical analysis plan.

8.5 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the KCC data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the KCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting

A Medical Monitor is assigned to this study at the Thomas Jefferson University. This is a physician/pharmacist who is not directly involved in the trial, and is not currently collaborating with the sponsor/investigator on any other trial. The role of the Medical Monitor is to review all reportable AEs/SAEs (in real-time) including grading, toxicity assignments, non-reportable AEs (quarterly), protocol violations/deviations, as well as

all other safety data and activity data observed in the ongoing clinical trial occurring at Thomas Jefferson University. The Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or termination of the study to the DSMC and TJU IRB.

Every KCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all unexpected and serious adverse events (SAEs) are reported to the TJU IRB and to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all unexpected and serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called. ***Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.*** A summary of the reporting requirements for KCC investigator initiated Phase I and Phase II studies are presented below.

AE/SAE's related to the study interventions are being tracked by the attending physicians caring for the patients in real time during their hospital stay and recorded on complication cards. This is also supplemented with chart review information. This data will be used to keep study intervention AE logs for each patient. After discharge, study subjects are continued to be tracked at the postoperative outpatient office visits up to 90 days post operation by the attending physicians.

We propose to submit to the DSMC for review all AE/SAE's specifically related to the WARP protocol interventions. These include, renal injury related to the volume restriction, injury related to enhanced physical therapy such as a fall, intolerance of the intervention (full liquid) diet with dizziness or lightheadedness. Given the fact that more than 50% of all pancreaticoduodenectomy patients develop some postoperative complication, such as pancreatic fistula, delayed gastric emptying, intraabdominal abscess, wound infection, urine infection, heart attacks, arrhythmias, pulmonary complications, renal, strokes, and deep vein thrombosis, and that these bear no relation to the specific interventions of the WARP protocol, they will not be reported to the DSMC.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 and 5
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at	Reviewed at	Reviewed at	5 Working Days	Reviewed at Quarterly	5 Working Days	Reviewed at Quarterly	Phase 1 - 48 Hours

	Quarterly DSMC Meeting and IRB Annual Review	Quarterly DSMC Meeting and IRB Annual Review	Quarterly DSMC Meeting and IRB Annual Review		DSMC Meeting and IRB Annual Review		DSMC Meeting and IRB Annual Review	(Death: 24 Hours) Phase 2 - 5 Working Days
Possible Probable Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 working days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase 1 - 48 Hours Phase 2 - 5 Working Days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 and Phase 2 - 48 Hours (Death: 24 Hours)

**NOTE: This table is based on the NCI AE/SAE reporting Guidelines and the TJU IRB Policy and Procedures. Please follow the individual protocol AE/SAE reporting guidelines if more stringent reporting procedures are specified.

8.5.2 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the KCC. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University KCC. The committee meets quarterly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call) within 24 hours following the notification of an unexpected adverse event felt to be related to the study drug.
- Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to

the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.

- A summary of the board's action is sent to each investigator, the CCRRC and TJU IRBs. The DSMC actions may include recommendations/requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the CCRRC. The DSMC provides the investigator with the rationale for any decision made.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the formal discontinuation of the study.

10.0 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.2.1 Independent External and Internal Audits

In addition to review by the DSMC, all studies initiated by KCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director of Clinical Investigations, KCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of

scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the CCRRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 STUDY FINANCES

12.1 Funding Source

Departmental funding as needed

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

13.0 PUBLICATION PLAN

There will be no sharing or publication of data other than that the overall results will be tabulated and published in a peer reviewed journal.

14.0 REFERENCES

15.0 APPENDICES