DATA AND SAFETY MONITORING PLAN
# MASSEY CANCER CENTER
## DATA AND SAFETY MONITORING PLAN

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1 INTRODUCTION

The VCU Massey Cancer Center provides oversight of clinical trials to ensure the safety of the research subjects and to ensure the integrity of the data collected and reported. The institution’s data and safety monitoring plan is established to comply with the National Institutes of Health policy (http://grants.nih.gov/grants/guide/notice-files/not98-084.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) and the Data and Safety Monitoring Plans Review Criteria issued 01/25/2011.

2 ORGANIZATIONAL STRUCTURE

2.1 Study Team (ST)

The Study Team (ST) is the group primarily responsible for study conduct, including data quality and subject safety. In most cases, the ST consists of the Principal Investigator, the Research Nurse and/or Clinical Research Associate, and the Study Biostatistician. The ST meets at regular intervals while subjects are on treatment to review study status. This review includes a summary of toxicities, including, but not limited to, reportable Adverse Events, and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment are addressed. All meetings are documented.

2.2 Data and Safety Monitoring Boards (DSMB)

The method and degree of monitoring is to be commensurate with the degree of subject risk and the size and complexity of the project. The Protocol Review and Monitoring Committee determines the appropriate plan, which may include a DSMB. To determine the appropriate plan, the PRMC first determines the level of risk.

Studies that involve minimal risk include the following:

- Nutritional
- Behavioral
- Exercise
- Psychosocial
- Low risk tissue sample collection
- Existing data

Data and Safety Monitoring Plans for such studies generally involve the PI and Study Team reviewing the data and ensuring adequate data monitoring and oversight of safety and data security issues. Such studies do not require a Data and Safety Monitoring Board.

Studies that involve greater than minimal risk include the following:

- Drug or biologic agent interventions
- Invasive devices
• Surgery
• Radiation
• High risk specimen collection

The predominance of investigator initiated trials are pilot, phase I, or phase 2 trials involving therapeutic intervention, prevention intervention, or an intervention for supportive care. The Cancer Center’s default plan for these investigator-initiated trials involving greater than minimal risk is assignment to an MCC DSMB as well as auditing by the Audit Committee.

2.2.1 Composition of DSMBs

Upon PRMC approval of a clinical trial that requires an MCC DSMB, the Chair of the DSMBs assigns the clinical trial to a previously constituted DSMB or creates a new DSMB as required by ongoing workloads. Chairs of individual DSMBs must have appropriate expertise; for example, DSMBs for therapeutic clinical trials are chaired by physicians with expertise in the modality. Other DSMB members are chosen from the MCC membership or staff in order to provide the DSMB with an appropriate breadth and depth of clinical trials expertise. A typical DSMB has additional expertise in Biostatistics, Data Management, and Research Nursing.

2.2.2 Conflicts of Interest

Members of a DSMB may not be investigators or other protocol staff for the trial it monitors.

2.2.3 Scheduling and Process of DSMB Reviews

Frequency of DSMB meetings depends on the level of risk as determined by the PRMC. In general, risk is related to phase of the trial.

- Phase I trials – DSMB typically meets quarterly.
- Phase I/II and Phase II trials – DSMB typically meets quarterly during the Phase I portion of the trial until the Maximum Tolerated Dose is determined, then semiannually during Phase II.
- Phase III – DSMB meets at least annually

Consideration also is given to other factors, such as

- Interventions that do not involve cytotoxic agents may be monitored semiannually.
- Radiation therapy trials that are known to involve late toxicities may be monitored semiannually.

As mentioned in Section 2.2.5, the DSMB reviews the latest report from the Audit Committee. Although the scheduling of the Audit Committee review and the DSMB meetings are independent, reports from the Audit Committee are sent to the DSMB Coordinator in real time. The Audit Committee report is distributed to the DSMB, who may decide to convene early to assess study progress or subject safety in light of Audit Committee’s findings.
The DSMB’s initial meeting occurs as soon as possible after the trial has received PRMC approval. The purpose of the initial meeting is to review the protocol and advise the principal investigator and study team of its expectations in regard to data to be available at its regular meetings, including the grades of adverse events that should be recorded, as well as its expectations for expedited reporting.

In all trials monitored by a local DSMB, serious adverse events or protocol deviations that are reportable to the IRB in an expedited manner are also reported to the DSMB via the DSMB Coordinator. The Coordinator distributes the report electronically to the trial’s DSMB Chair, who reviews the report and determines if the DSMB should convene early to review the event.

If the DSMB decides during the course of the trial that the prescribed meeting schedule is too frequent, it would request that the Study Team revise the protocol to include a different meeting schedule. The protocol revision must be approved by PRMC and the IRB prior to changing the meeting schedule.

2.2.4 Confidentiality of data

The data is reviewed in such a manner that subject confidentiality is maintained. The DSMB members are able to review data from individual subjects, who are identified by only Study ID Numbers. Patient identifiers are not displayed. Blinded treatments are rarely an issue due to the portfolio of trials at the Massey Cancer Center. However, if a DSMB were responsible for monitoring a phase 3 trial that involved blinded treatment arms, the nature of each arm would be protected until such time as it is determined that unblinding is necessary to protect the safety of the subjects.

2.2.5 Focus of Review

DSMBs evaluate ongoing trials for the following factors that can affect study outcome:

- study progress
- study integrity
- early stopping rules
- observed adverse events

To facilitate the review, the DSMB uses the following tools:

- Audit Committee reports
- Report from the Study Team
- Data entered into the Oncore Clinical Trials Management System, including enrollment rate, reasons for subject discontinuation, observed adverse events, and protocol deviations

Chairs of individual DSMBs review expedited reports of adverse events in real time and convene special meetings of the DSMB if appropriate.

2.2.6 DSMB Reports

DSMB recommendations are reported to the Principal Investigator and Study Team, and the IRB. If the DSMB has concerns that need correction or clarification, the
The board may decide to meet earlier than scheduled to determine if the concerns have been addressed. If a DSMB identifies problems so serious as to raise doubts about the meaningfulness of the results of a trial, it also reports its findings to the PRMC, which has authority to suspend or close the trial.

Reports also are sent to the Chair of DSMB chairs to ensure consistency of monitoring across individual DSMBs. If the Chair sees issues that he is concerned about, he may take his concerns to the Director of the cancer center.

If affiliate sites are involved in the trial, a copy of the report would be distributed to the sites for submission to their IRBs.

### 2.3 Audit Committee

Multi-center studies initiated elsewhere commonly have an independent auditing process and generally are not subject to Massey audits.

Investigator initiated trials involving more than minimal risk as determined by the Protocol Review and Monitoring Committee, including locally-initiated multi-center studies, are subject to Massey audits. In all cases, a trial that has been specified to be monitored by an independent Data and Safety Monitoring Board is also subject to audit by the Audit Committee.

The Audit Committee also is responsible for review of Massey’s subjects enrolled in multicenter consortia trials such the Southeast Phase 2 Consortium. The Consortium provides for a central Data and Safety Monitoring Committee; however, participating sites are required to audit charts from its subjects and provide such reports to the Moffitt Cancer Center, which is the Coordinating Center for the Consortium.

In addition, the Audit Committee reviews the research conducted at its research affiliates.

#### 2.3.1 Composition of Audit Committee

The Core Audit Committee consists of the Chair from the Biostatistics Shared Resource, a physician, and members with expertise in data management and regulatory affairs.

Audit Committees specific for each study are constituted by the Chair of the Core Audit Committee from the members and staff of the Massey Cancer Center, and VCU faculty in a manner that avoids conflicts of interest. Each Audit Committee consists of the Chair (or his or her designee), a Physician, a Regulatory Expert, a Research Nurse and/or a Clinical Research Associate.

#### 2.3.2 Conflicts of Interest

Members of an Audit Committee may not be investigators or other protocol staff for the trial.

#### 2.3.3 Focus of Review by the Audit Committee

Audits focus upon:

- PRMC, IRB and extramural regulatory agency compliance, including verification of study personnel's human subjects protection training and other credentials
• Chart review, including
  • Documentation of subject eligibility
  • Documentation of study endpoints
• Treatment intervention
• Drug accountability (if applicable)
• Adequate communication with participating institutions in multi-center trials
• Study Team performance including documentation of study team meetings
• Adverse Event Reporting, including distribution of reports to participating sites

2.3.4 Scheduling and Process for Audits

Frequency of audits is specified by the PRMC at the time of study approval. Unless otherwise specified by the PRMC, a first audit is conducted upon enrollment of a third subject and includes at least one subject chart from each participating site if the trial is multicenter. Subsequent audits are conducted at least yearly and more frequently at the discretion of the Audit Committee or directive of the DSMB or the PRMC.

Affiliate sites that have not been previously audited by MCC are audited within 3 months of enrollment of the first patient at the site.

The Study Team is notified two weeks prior to the audit of the research charts selected for audit. In general, charts from three subjects or one subject from each participating site, whichever is greater, are reviewed in an audit. Regulatory documentation, investigational drug accountability forms, and research charts are made available on the day of audit. A sample of the Audit form is included in Appendix B.

2.3.5 Audit Committee Reports

The Audit Committee report is issued to the Principal Investigator and the DSMB. The Director for Clinical Research reviews a summary of audit results on a quarterly basis and presents the summary to the Clinical Trials Operations Committee (CTOC), composed of the Associate Director for Clinical Research, the Chief Administrative Officer for the Cancer Center, the Administrative Director for Research and Operations, the Administrative Director for Clinical Research, and the Research Nurse Supervisor.

2.4 Protocol Review and Monitoring Committee (PRMC)

Virginia Commonwealth University requires that all cancer-related research studies must be reviewed and approved by the Massey Cancer Center Protocol Review and Monitoring Committee prior to IRB submission. Although they review the same materials, PRMC review focuses upon science, whereas IRB review focuses upon protection of human subjects. Initiation and continuation of a study requires ongoing approvals by each regulatory authority, and each has the authority to suspend or terminate a study.

Research studies subject to PRMC review include the following:
  • Studies involving patients with cancer, their families or their health care providers.
• Studies involving secondary data regarding cancer patients or their medical records.

• Cancer-related surveys (e.g., attitudes about risk, prevention and treatment) of the general population.

The PRMC serves two main functions:

• Conduct an initial and ongoing evaluation of the scientific merit and scientific progress of all cancer-related clinical research conducted at VCU.

• Establish priorities among studies potentially competing for patients or research resources.

2.4.1 Composition of PRMC

The Chair and Members of the PRMC are chosen by the Massey Director upon the advice of the Associate Directors. Membership is balanced to assure the presence of basic, clinical, and cancer prevention and control expertise as well as expertise in biostatistics, research nursing, and pharmacy issues. Staff members of the Office for Clinical Research manage the administrative functions of the PRMC and its subcommittee.

The chair of the PRMC proposes new members to the Associate Directors, who then make recommendations to the Director. As part of an annual review of committee members the chair and senior leaders consider the qualifications and experiences of new members to the Center and propose those best suited for the PRMC be rotated onto the committee. The Director reappoints committee members annually.

MCC has an expanded mandate to review all VCU cancer-related clinical research, including research that does not constitute a clinical trial. Given the increased volume of studies and the diversity of activities, MCC established a subcommittee of the PRMC to specifically review Cancer Prevention and Control (CPC) clinical research. As CPC clinical research may potentially compete with clinical trials for MCC resources or patients, final prioritization of clinical research is the responsibility of the PRMC. The CPC Subcommittee rotates up to two of their members to participate at the PRMC meetings as needed.

The PRMC has broad representation from the Schools, Departments and Divisions conducting cancer-related clinical research throughout VCU. The PRMC routinely has representation from the Departments of Internal Medicine (Hematology, Oncology & Palliative Care, Quality Health Care), Obstetrics-Gynecology (Gynecologic Oncology), Pediatrics (Hematology/Oncology), Radiation Oncology, Surgery (Surgical Oncology), Social and Behavioral Health (Cancer Control & Oncology Administration), Psychology, Health Administration, Nursing (Family & Community Nursing & Adult Health Nursing), Biostatistics, and Pharmacy. Any Dean or Chair of a School, College, or Department conducting research that is subject to PRMC Committee oversight may request the appointment of a faculty member to the PRMC Committee.

A Parent Committee quorum requires attendance of a minimum of five physicians and one biostatistician, and actions require a majority vote of a quorum.

Members of the Cancer Prevention and Control Subcommittee have specific expertise in social and behavioral research, psychological research, genetics
research, health economics research, health services research, and symptom and toxicity management research.

2.4.2 Conflicts of interest

Virginia Commonwealth University’s Office for Research assumes global responsibility for review and management for potential conflicts of interest that might affect institutional human subjects research.

Persons with a conflict of interest relative to the trial under review, e.g., investigators or other protocol staff, may not serve as PRMC’s primary, secondary, or biostatistical reviewer. Members and guests with a conflict of interest may participate in preliminary discussions of a protocol, but they must not be present during concluding discussion and voting.

Study revisions and interim reports of studies for which the PRMC Chair or other committee member is a participating investigator are reviewed by another member of the committee.

2.4.3 Elements reviewed by PRMC at initial review:

Data and safety monitoring plan – presence and adequacy of a data and safety monitoring plan for clinical trials. The method and degree of monitoring is to be commensurate with the degree of subject risk and the size and complexity of the project.

Studies that involve minimal risk include the following:

- Nutritional
- Behavioral
- Exercise
- Psychosocial
- Low risk tissue sample collection
- Existing data

Data and Safety Monitoring Plans for such studies generally involve the PI and Study Team reviewing the data and ensuring adequate data monitoring and oversight of safety and data security issues.

Studies that involve greater than minimal risk include the following:

- Drug or biologic agent interventions
- Invasive devices
- Surgery
- Radiation
- High risk specimen collection

The Cancer Center’s default plan for investigator-initiated trials involving greater than minimal risk is assignment to an MCC DSMB. Such trials also are required to
be audited by the Audit Committee. Investigators may propose and must justify alternative plans.

**Rationale** or **Introduction** – description of current knowledge with attention to the value of addressing the study objectives. Problematic or potentially controversial aspects of the study design should be addressed. Long term objectives and plans may be described.

**Specific objectives** - clear and quantifiable objectives, with a primary objective identified in the case of multiple objectives.

**Agent/device information** - including supplier, storage, stability, formulation, preparation, administration/delivery, known and potential adverse events.

**Study Population** - Generally defined by eligibility/ineligibility criteria.

**Exclusion of any of the following special populations** - women, children, minorities -- must be justified scientifically.

**Study design** - should correspond with objectives; all objectives should be addressed by the study design, and all elements of the study design should relate to the objectives.

**Enrollment procedure** – a specific procedure should be described that indicates enrollment authority and clarifies the time point at which a patient becomes a subject.

**Description of the study intervention** – complete, concise, and clear description in terms of the management of individual subjects (diagnostic evaluation, study intervention, subject monitoring, outcome assessment), with anticipated problems addressed.

**Description of study procedures** – complete, concise, and clear description in terms of patient cohorts, identification of intermediate and final study endpoints, schedule of events, interim analyses, etc. Quality of life and other **instruments** must be included for review.

**Sample Size and Accrual** - Should describe and justify the expected sample size numerically and/or operationally and the projected accrual rate. For investigator-initiated trials, including MCC investigator-initiated multi-center trials, primary responsibility for timely accrual resides with the investigator. PRMC has a general expectation that the total accrual time should not exceed two years; longer projected accrual times should be justified. For other multi-center research, primary responsibility for timely accrual resides with the sponsor. In general, there is an expectation that such studies will accrue at least two MCC subjects per year; exceptions should be justified.

**Data collection and analysis plan** – description of transfer of clinical data to a research database for analysis, the analytical plan specifically addressing relevant biostatistical issues, and plans for interim analysis to be provided to the PRMC when appropriate.

**Confidentiality** – strategies for maintenance of confidentiality.
**Accrual rate** – rate of accrual should be projected. In general, PRMC anticipates that study enrollment periods (time elapsed from first to final patient enrollment) will not exceed two years. Investigators must propose an acceptable method of real time accrual reporting. PRMC monitors studies for both excessive accrual and inadequate accrual rates.

**Adverse Events, Definitions and Reporting** - Should describe procedures for the identification, characterization, and reporting of adverse events, including identification and timely reporting of events requiring expedited reporting.

**Informed Consent Form** - The consent form is reviewed to assure that study procedures and risks are appropriately described from a scientific standpoint.

**Research Infrastructure** – description showing adequacy of infrastructure. All study investigators must have updated curricula vitae, medical licenses, and DEA licenses, if applicable, on file in the Office for Clinical Research. All investigators and clinical research personnel must have completed the human subjects protection training course and filed conflict of interest statements, if applicable.

**Study Biostatistician** - An expert biostatistician must be named as an investigator on all investigator-initiated protocols.

2.4.4 Ongoing Review by PRMC

Ongoing review consists of review of amendments, accrual, and reports of the Data and Safety Monitoring Board (DSMB) if serious concerns are identified. Accrual is reviewed at least annually with the progress review of the trial. Accrual to investigator initiated trials is reviewed six months after initial PRMC approval.

2.4.5 Early Termination of a Trial

Trials may be terminated early on the basis of accrual, prioritization, or a report from the Data and Safety Monitoring Board indicating that problems exist with the clinical trial conduct that are so serious as to render the results of the clinical trial meaningless. Ongoing trials are reviewed for accrual at least annually. For investigator-initiated trials, including MCC investigator-initiated multicenter trials, primary responsibility for timely accrual resides with the investigator.

For other multicenter research, primary responsibility for timely accrual resides with the sponsor. MCC reviews accrual to such studies from the standpoint of efficient use of MCC resources. In general, there is an expectation that such studies will accrue at least two subjects per year. In the case of protocols not meeting this expectation, the PI is notified that the protocol is subject to termination. Investigators may provide additional information and/or appeal a PRMC decision to terminate.

2.4.6 Appeals

Investigators who disagree with the PRMC’s decision may appeal the decision to the committee. The appeal is generally in writing; however, the investigator is invited to attend the PRMC meeting to discuss the issues.
3 ADVERSE EVENT REPORTING

Adverse event reporting requirements are a function of the regulatory authorities relevant to a particular study and may be quite complex. PRMC review includes a review of the adequacy of adverse reporting plans. Definitions of reportable adverse events and who issues and receives reports must be described in a protocol.

Adverse events routinely are reviewed by DSMBs at the time of ongoing reviews.

Adverse events subject to expedited reporting as specified by relevant regulatory authorities or sponsors also must be reported to the DSMB in an expedited manner.

For multi-center studies for which the Cancer Center is the Coordinating Center, a mechanism must be in place for timely receipt of reportable events from participating centers and distribution of reportable events to all participating centers.

See:

- [http://www.wirb.com/content/inv_adverse_events.aspx/](http://www.wirb.com/content/inv_adverse_events.aspx/) for WIRB adverse event reporting requirements.

4 NOTIFICATION TO SPONSOR OF SUSPENSION OR TERMINATION OF A TRIAL

Trials may be terminated by the PRMC under the following circumstances:

- Progress review showing accrual not meeting the stated goals in the study protocol or the minimum accrual required by the PRMC.

- Recommendation of the DSMB in the case of serious concerns.

In general, Principal Investigators for studies considered for termination are provided the opportunity to correct deficiencies in accrual and study performance. Ongoing deficiencies in these areas result in termination. A copy of the notification of termination is sent to the IRB.

If an NCI-funded trial or investigator is suspended or terminated, a copy of the letter is distributed to the Massey Cancer Center’s Director of Research Administration & Operations to notify the Program Director responsible for funding the trial.
## APPENDIX A

### Institutional Oversight of Cancer Related Clinical Research

**Massey Cancer Center**

All Components are responsible to the Director

<table>
<thead>
<tr>
<th>Component*</th>
<th>Responsibilities</th>
<th>Authorities</th>
<th>Correspondence/Reports/Recommendations Go To</th>
<th>Composition</th>
</tr>
</thead>
</table>
| PRMC       | • Initial and ongoing review of scientific merit and scientific progress  
            • Establishment of priorities among trials | • Approve, suspend, terminate studies | • PI  
            • IRB  
            • MCC Director of Research Administration & Operations if closure/suspension notification to sponsor is required  
            • MCC Associate Director for Clinical Research | • Clinical Investigators  
            • Physician Scientists  
            • Biostatisticians  
            • Pharmacists  
            • Research Nurse  
            • Support from the Clinical Research Shared Resource (CRSR) |
| DSMB       | Ongoing review for assessment of  
            • Study progress  
            • Study integrity  
            • Early stopping rules  
            • Observed adverse events | • Reports  
            • Recommendations | • PI  
            • IRB  
            • Chair of DSMBs  
            • PRMC (only if has serious concerns about trial progress) | • Physician Chair  
            • Biostatistician from Biostatistics Shared Resource  
            • Clinical Research Associate from CRSR  
            • Research Nurse from CRSR  
            • 3 standing board members in administration/data management |
| Audit Comm | Ongoing assessment of  
            • Regulatory compliance  
            • Protocol compliance  
            • Trial interventions  
            • Collection of outcome data  
            • Adverse event reporting | • Reports  
            • Recommendations | • PI  
            • DSMB | • Data Management Expert Chair  
            • Physician from Massey Membership  
            • Regulatory Experts from CRSR  
            • Clinical Research Associate from CRSR  
            • Research Nurse from CRSR  
            • 2 standing board members in administration/quality control |
| VCU        | | | |
| IRB        | • Initial/ongoing review with regard to protection of human subjects | • Approve, suspend, terminate | • PI | • Membership from the VCU Faculty and Staff, and the Community |

*Composition is subject to change.*
APPENDIX B  AUDIT FORM
Audit Form – Study ID
Date:  

## Study Team

<table>
<thead>
<tr>
<th>Team Position</th>
<th>Team Member</th>
<th>CITI Training Expiration</th>
<th>Medical Licenses Expiration</th>
<th>CVs Expiration</th>
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<tbody>
<tr>
<td>Principal Investigator</td>
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<td>Study Site Contact/ Research Nurse</td>
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<tr>
<td>Research Nurse</td>
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<td>Data Manager; CRA</td>
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<td>Regulatory Coordinator</td>
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<td>Sub-investigator</td>
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<td>Sub-investigator</td>
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Has study team changed from currently approved protocol?  Y/N
Has the study team met?
How frequently?
According to protocol?
Documented?

### A. Subjects Reviewed

<table>
<thead>
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<th>Subject Initials / ID No.</th>
<th>Audit Verification: Eligibility, Pre-Treatment, Course 1</th>
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<td>Subject ID:</td>
<td>On Study Date:</td>
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**B. Informed Consent Validation:**

<table>
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<th>Version and/or date of applicable Consent Form</th>
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<table>
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<th>Consent Form signed and dated by subject?</th>
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<th>Consent Form signed and dated by clinician?</th>
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<th>Consent Form signed and dated by witness?</th>
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<th>Original copy of ICF in file?</th>
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**C. Eligibility**

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<th>Version and/or Date of applicable protocol</th>
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<tr>
<th>Have all eligibility criteria been met? (See Elig Criteria)</th>
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<th>List Eligibility Criteria not met</th>
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</table>
## Massey Cancer Center
### Audit Form

**Subject ID:**

**On Study Date:**

### D. Intervention According to Protocol

- Have all procedures/laboratory tests been performed on schedule?
- Any deviations from treatment protocol that could make Subject not evaluable?
- Did Subject withdraw from study early or prematurely terminated from study?
- Are reasons for withdrawal or termination documented?

### Have all SAEs been reported as required?

### Is sufficient information documented to support attribution?

### F. Drug Accountability

- Are pharmacy dispensing records in order?
- Do all subjects have adequate documentation of medication usage?
- Can dispensing and administration data be correlated?
### G. Protocol Violations/Deviations

Any significant protocol deviation(s) or violation(s) detected at this audit?

If so, were the deviation(s) or violation(s) reported/documentated by the study team?

### H. Other Study Issues

Has any un-blinding been required and documented?

Has randomization been maintained?
APPENDIX C

Information Flow

Director, Massey Cancer Center

Associate Director for Clinical Research

Clinical Trials Operations Committee

Chair of DSMBs

Director of Research Administration & Operations

PRMC

DSMB

Audit Committee

Principal Investigator/Study Team

VCU IRB

If closure or suspension notification to sponsor is required

Only if serious concerns about study progress are identified