Institutional Data and Safety Monitoring (DSM) Plan

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Synopsis

The Alvin J. Siteman Cancer Center (SCC) places the highest priority on ensuring the safety of patients participating in clinical trials. The Director holds the overall responsibility for data and safety monitoring within Siteman Cancer Center. Oversight of study-specific data and safety monitoring is the responsibility of two committees within SCC: the Protocol Review and Monitoring Committee (PRMC) and the Quality Assurance and Safety Monitoring Committee (QASMC). Every clinical trial conducted at SCC must also include a study-specific plan for data and safety monitoring. The contents of each protocol's monitoring plan and its associated reporting requirements are dependent upon the degree of risk encountered by patients on the study, the study sponsor, the nature of the investigational agent (if applicable), and the phase of the trial.

The PRMC is responsible for the scientific review of all cancer-related trials throughout a study's lifetime, from time of initial submission through each amendment and annual renewal until the study is closed with the PRMC. The QASMC, which serves as the SCC's Data and Safety Monitoring Committee (DSMC), provides independent oversight and review of quality assurance audits, unanticipated problem (UP) reporting, and interim data and safety monitoring (DSM) reports for local investigator-initiated trials (and other trials as requested). According to relevant federal requirements, the QASMC may require that a study convene an *ad hoc* Data and Safety Monitoring Board (*ad hoc* DSMB) or make use of the SCC independent standing Data and Safety Monitoring Board (SCC independent standing DSMB).

This document outlines the policies established by the SCC for the appropriate oversight and monitoring of the conduct of oncology clinical trials. The purpose of these policies is to ensure both the safety of study participants and the validity of clinical trials data.

Acknowledgements

The SCC is greatly indebted to efforts of the National Institutes of Health, particularly the National Cancer Institute, whose data and safety monitoring policies and plans formed the basis of our data and safety monitoring plan. We also acknowledge the generosity of the Ohio State University Comprehensive Cancer Center and the Yale Comprehensive Cancer Center for willingly sharing their data and safety monitoring plans when this plan was first developed in 2001.

Definitions

Clinical trial: SCC, for purposes of this policy, has adopted the NIH definition of a clinical trial: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (https://grants.nih.gov/policy/clinical-trials/definition.htm)

A *behavioral trial* is a study in which either (a) the intervention employs behavioral strategies, procedures, or theory, or (b) the primary outcomes involve behavior change on the part of patients, clinicians, families, or larger systems (e.g. change in worksite policies). Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not clinical trials.

Intervention: An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. (Examples include (but are not limited to): drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies.) (https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm)

Health-related biomedical or behavioral outcome: A health-related biomedical or behavioral outcome is defined as the pre-specified effect of an intervention on the study subjects. Examples include positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); disease processes; health-related behavior; and well-being or quality of life. (https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm)

Conflict of interest: Individuals invited to serve on QASMC and the SCC independent standing DSMB as either voting or non-voting members will disclose any potential conflicts of interest, whether real or perceived, to the faculty chair of the committee/board and/or his/her designee/project manager, as well as to the appropriate institutional officials(s) in accordance with the institution's policies. Conflict of interest can include financial interest, professional interest, proprietary interest, and miscellaneous interest. A financial conflict of interest refers specifically to a situation in which it is reasonably determined that a material financial interest could directly and significantly affect the design, conduct, or reporting of research. (https://research.wustl.edu/determining-and-managing-research-fcois-procedures/) Potential conflicts which develop during a member's tenure on a committee must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in QASMC or the SCC independent standing DSMB will be made in accordance with the institution's policies.

Unanticipated problem: An unanticipated problem involving risks to participants or others includes any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document and (b) the characteristics of the subject population being studied
2. related or possibly related to participation in the research (meaning that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

(https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#Q1)

Data and safety monitoring plan (DSM plan): A data and safety monitoring plan is a plan which contains the required elements for tracking and reporting data and safety information for a given study.

Data and safety monitoring board (DSMB): A data and safety monitoring board is a group of investigators who are familiar with a specific research protocol and its plans for data and safety monitoring. They review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated. They also review trial performance information such as accrual volume and rate, and determine whether and to whom outcome results should be released prior to the reporting of study results. They review reports of related studies to determine whether the monitored study needs to be changed or terminated, and they review major proposed modifications to the study prior to their implementation. (https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf)

Organization and Administration

As monitoring and reporting requirements vary depending on the size and complexity of the trial, degree of risk encountered by study participants, the study sponsor, the type of agent or agents involved, and trial phase, the responsibility to ensure that monitoring is timely and effective is shared by a number of SCC offices. The Director holds the overall responsibility for data and safety monitoring within Siteman Cancer Center. Other individuals and units with responsibilities in data and safety monitoring include the Protocol Review and Monitoring Committee (PRMC), the Quality Assurance and Safety Monitoring Committee (QASMC), the Washington University Institutional Review Board (IRB), individual *ad hoc* data and safety monitoring boards (*ad hoc* DSMBs) for trials, the Siteman Cancer Center independent standing DSMB, the principal investigators of NIH grants, and other principal investigators of individual clinical trials. This institutional data and safety monitoring plan is tailored to ensure monitoring of all clinical trials, meet the reporting requirements of individual trial sponsors, ensure that monitoring is timely and effective and that those responsible for monitoring have the appropriate expertise, and eliminate excessive or redundant monitoring and reporting.

Monitoring Trial Progress and Patient Safety

All clinical trials conducted at Siteman Cancer Center must include provisions for data and safety monitoring.

The extent of monitoring varies by the phase of the trial, size and complexity of the trial, degree of risk encountered by patients on the study, the study sponsor, the type of agent or agents involved, and the phase of the clinical trial. This document was developed to coordinate and provide oversight for data and safety monitoring for all cancer-related trials consistent with the National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1998 (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) with further guidance issued on June 5, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). The National Cancer Institute issued a policy on June 22, 1999 for data and safety monitoring of all trials with the additional requirement that randomized phase III trials be monitored by *ad hoc* Data and Safety Monitoring Boards (*ad hoc* DSMBs) (https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf).

Currently, all SCC clinical trials undergo data and safety monitoring. Study investigators and clinical trials staff forward all unanticipated problems to the Washington University Institutional Review Board (IRB) and the study sponsor, and the Siteman Cancer Center Quality Assurance and Safety Monitoring Committee (QASMC) reviews all unanticipated problems for investigator-initiated protocols.

Required Elements for Protocol-Specific Data and Safety Monitoring Plans

All clinical trials conducted at SCC must have a satisfactory DSM plan described in detail in the protocol and/or IRB application. The DSM plan is assessed by the Protocol Review and Monitoring Committee (PRMC) as part of its review process and is confirmed by the Washington University IRB during its review. Each study-specific DSM plan must include:

- Delineation of oversight responsibilities (i.e. whether data and safety information will be reviewed by the sponsor, PI and study team, PI and study team plus SCC's Quality Assurance and Safety Monitoring Committee (QASMC), or PI and study team plus QASMC plus *ad hoc* Data and Safety Monitoring Board (DSMB) or SCC independent standing DSMB)
- Description of data and safety review process
- Timeframe for submission of data and safety information to the responsible parties
- Description of adverse event reporting requirements and procedures

The DSM plan for all phase III randomized trials supported by NCI, all multisite clinical trials involving interventions that entail potential risk to participants, and all trials with a blinded treatment arm must include monitoring by a DSMB. A DSMB may also be convened for other trials as required by the QASMC, PRMC, or PI.

Protocol Review and Monitoring Committee (PRMC)

A Protocol Review and Monitoring System is required for all NCI-designated Cancer Centers; the Protocol Review and Monitoring Committee (PRMC) serves in that capacity at SCC. The PRMC fulfills the NCI expectation that all NCI-designated cancer centers scientifically evaluate and prioritize all cancer center trials derived and supported from institutional sources, including those originating from other cancer centers or from industry. The PRMC also provides a mechanism for monitoring all cancer research studies in the institution for scientific progress, carrying with it the authority to close any studies that are not making sufficient scientific progress or meeting accrual or performance standards.

The primary goal of the PRMC is to ensure that all cancer-related research studies involving human subjects conducted under the auspices of the SCC are scientifically and statistically sound, appropriately designed, feasible for completion, and, if applicable, in compliance with NIH guidelines for clinical trials, including monitoring for accrual and undue toxicity. It is responsible for:

- Providing scientific peer review for all institutional and industry-initiated cancer research studies
- Ensuring proper study design
- Reviewing all active cancer research studies for renewal/termination
- Reviewing accrual in all active cancer research trials

The PRMC is not intended to duplicate, or overlap with, the responsibilities of the IRB, nor is it intended to audit for quality control or safety reasons.

PRMC Committee Structure

The SCC PRMC consists of a representative group of basic researchers, clinical researchers, population scientists, and staff with diverse areas of expertise. Membership includes medical, surgical, and radiation oncologists; behavioral scientists; psychologists, biostatisticians; nurses; pharmacists; data managers; patient advocates; and a member of our protocol development staff. Members are invited by the Director of SCC to serve a two–year term and may be reappointed for additional terms. They are selected based on the experience they have in designing or conducting clinical trials or based on special clinical expertise. A complete and current roster may be found on the PRMC website (https://siteman.wustl.edu/research/resources-for-researchers/protocol-

review-and-monitoring-committee/). While there may be minimal overlap, PRMC representation does not duplicate that of the QASMC, and the same individual does not chair or have supervisory responsibility over both committees. The Clinical Protocol and Data Management leader does not chair and is not a member of the PRMC.

PRMC Review Process

There is a single PRMC that meets three times per month to review all proposed cancer-related research conducted at the SCC and the Washington University Medical Center (Washington University School of Medicine, Barnes-Jewish Hospital, and St. Louis Children's Hospital). All new interventional trials receive full committee review unless they have previously undergone CTEP, NIH, or similar peer review, in which case they are administratively reviewed by one of the PRMC Co-Chairs. Non-SCC-led investigator-initiated studies that have received PRMS review at an NCI-designated Cancer Center in good standing are also administratively reviewed, as well as registries, retrospective studies, specimen collections, and other studies that are not interventional trials.

At the time of submission, a study is assigned to the next available meeting, with the exception of behavioral science studies, which are shunted to the Behavioral Sciences Subcommittee (BSS) of the PRMC. The BSS was created in January 2006 to review all behavioral science studies that involve cancer. Its membership includes reviewers with appropriate expertise for the evaluation of protocols determined to be of a behavioral nature by the PRMC Co-Chairs. BSS review is comparable to other PRMC reviews, but its emphasis is on the review of studies that focus on primary or secondary cancer prevention behaviors, quality of life in cancer patients, and epidemiological data related to cancer control, prevention, or incidence, as well as studies that involve extensive use of psychological questionnaires.

PRMC Quorum Requirements

In order for a PRMC meeting to begin, quorum must be met. Quorum is defined as attendance of at least one co-chair, one statistical reviewer, and at least 50% of the number of full members associated with that meeting day. (There are three meetings per month, and each member is associated with one of those meeting days. Therefore, quorum for a given meeting is not defined as attendance of 50% of the entire PRMC membership, but attendance of 50% of the full members who would be expected to attend a particular meeting. Both full and *ad hoc* members are counted when determining whether attendance for quorum has been met.).

PRMC Assurance of Confidentiality during Review

In general, no communication, either written or oral, of the deliberations or recommendations of the committee will be made outside of the committee except as provided for in the PRMC policies and procedures. Each member of the PRMC must sign a statement of confidentiality.

PRMC Full Committee Review

All new studies that meet the criteria for full committee review and are received on or prior to the submission deadline will be placed on the agenda for the next committee meeting. The submission must include all study documents: complete protocol, draft consent form, relevant investigator brochure(s) and/or package insert(s), pharmacy manuals, questionnaires, data collection forms or data dictionary (for local investigator-initiated trials), draft IRB application, and completed Research Focus Group form with applicable leader signature. In addition, the study protocol must contain a study-specific DSM plan outlining the procedures for review of study data for integrity, accuracy, and safety purposes. All clinical trials are required to have a specific DSM plan appropriate to the size and complexity of the trial. The degree of monitoring is dependent upon the phase of the trial, degree of risk, complexity of the trial, study sponsor, nature of the investigational agent, and phase of the trial. **No study receives PRMC approval without a DSM plan.** The PRMC also reviews data collection forms or a data

dictionary for local investigator-initiated trials to verify that the study objectives will be assessable based on the data collected.

Each study scheduled for full committee review is reviewed by two physician reviewers, a biostatistician, and a patient advocate. Depending on the type of study, it will also be reviewed by a pharmacist, a behavioral scientist, a nurse, a data manager, and/or a representative from SCC's Protocol Development group. The individuals best qualified for review of each study are assigned as reviewers by PRMC staff, with assignments approved by committee co-chairs and conflicts of interest taken into consideration when making review assignments so that PRMC members who are listed on the study team for a submission are not assigned as a reviewer. The primary reviewer is responsible for summarizing the merits and weaknesses of the study for presentation to the full committee. In the event that the primary reviewer is absent, the secondary reviewer or committee co-chair will present the study to the committee. For each study, the assigned reviewers each complete an electronic Protocol Evaluation Form specific to their field of review. In addition, the reviewers are encouraged to contact the principal investigator before the meeting if there are questions regarding study design or other issues.

After full committee discussion, the committee will make one of the following determinations:

1. Approved or approved with comments
2. Contingent approval
3. Deferred
4. Disapproved

Members of the committee with a conflict of interest on a particular submission are required to recuse themselves from voting on the determination for that submission.

PRMC Full Committee Review Feedback and Follow-Up

A letter from the committee stating the determination is sent to the PI and study submitter. For protocols that receive a contingent approval or deferred determination, investigators are expected to submit a point-by-point response to the PRMC within 60 days. This response must include tracked changes versions of all revised documents.

PRMC review of new studies occurs prior to IRB review. A new protocol will not be reviewed or approved by the IRB until all PRMC concerns are satisfactorily addressed and PRMC approval has been communicated to the Washington University IRB.

PRMC Administrative Review

For new studies that meet the criteria for administrative review, the PI must submit a complete application as outlined above. Studies that have received prior scientific approval at an NCI-designated Cancer Center must include documentation of the approval and documentation that the PRMS of that center is in good standing with the NCI with the submission package. The PRMC staff will verify that the study meets administrative review requirements, after which it will be forwarded to a PRMC co-chair for review.

For revisions that meet the requirements for administrative review, the PI must submit the revised study documents, a clearly delineated summary of changes with justification for the changes, and IRB documentation as applicable. Without a clear justification for the amendment, the submission will be returned for more information. Substantive scientific changes to the protocol should receive PRMC review prior to implementation; these will be flagged as requiring full committee review and will be scheduled for the next available meeting; it is recommended but not required that modifications of this nature undergo PRMC review prior to IRB review. Minor or administrative changes to the protocol may be simultaneously reviewed by the PRMC and IRB. Once a study is closed with PRMC, no further reviews are required.

PRMC Review for Progress and Safety of Participants

For annual renewals, continuing review documentation must be submitted to PRMC no later than the time of IRB approval of the continuing review. The application must include the number of patients consented and treated, a summary of unanticipated problems reported to date, and rationale for continuation of study. For interventional investigator-initiated studies, continuing review documentation must include a copy of the most recently approved DSM/DSMB report and annual QA audit report (if applicable). Once a study is permanently closed to accrual and all participants are off active intervention, a study may be closed with PRMC with no further reviews required.

Termination by PRMC

The PRMC may terminate a study if recommended by the QASMC, the IRB, and/or the SCC Director (e.g. due to low accrual, unacceptable minority accrual, inadequate retention, egregious noncompliance, or excessive adverse events); the PRMC also has the authority to terminate a study based on its own review.

PRMC Policies and Procedures

The PRMC's full policies and procedures document may be found on its website:
https://siteman.wustl.edu/research/resources-for-researchers/protocol-review-and-monitoring-committee/

Quality Assurance and Safety Monitoring Committee (QASMC)

A means of ensuring that all research data generated under SCC's sponsorship are of high quality, reliable, verifiable, and reproducible is required in order to maintain NCI designation. The Quality Assurance and Safety Monitoring Committee (QASMC) fulfills that function, serving as the SCC Data and Safety Monitoring Committee (DSMC) and providing independent oversight of clinical trials conducted at the SCC. It ensures that monitoring is timely and effective, and that those responsible for monitoring have the appropriate expertise.

The primary goal of the QASMC is to oversee the data and safety monitoring of investigator-initiated trials. It is responsible for:

- Reviewing routine data and safety monitoring (DSM) reports, which are typically submitted semi-annually
- Arranging for QA Advisors from their roster to provide expertise for QA audits
- Performing QA audits
- Assessing the trial audit findings of investigator-initiated therapeutic trials (and others audited at the request of the PRMC) performed by the QA Auditors and Advisors
- Making recommendations to the study team based on the audit findings
- Reviewing all Unanticipated Problems occurring on investigator-initiated interventional trials at SCC

QASMC Oversight Based on Degree of Risk, Size, and Complexity

QASMC assesses the frequency and necessity of performing QA audits based on the study-specific metrics of degree of risk involved for the participants as well as the size and complexity of the trial. For example, studies involving first-in-human drugs or devices, gene therapy, or other novel interventions are generally audited by QASMC more frequently than studies such as diagnostic imaging. Additionally, standard data and safety monitoring language exists for insertion into investigator-initiated protocols that is customized by study phase, with phase I studies describing frequent monitoring (monthly or sooner) and phase II and III studies describing regular but less frequent monitoring (every 6 months). Complexity of management is also a factor that produces different levels of oversight, with template language for multi-institutional trials, high-enrolling trials, and trials with blinded treatment arms outlining the specific processes by which the PI will receive and review safety data and including

semiannual DSMB meetings. The QASMC coordinates with PRMC in suspending and/or closing trials to patient accrual should the risk to patients be excessive or outweigh the potential benefits of the study.

QASMC Committee Structure

The SCC QASMC includes medical, surgical, and radiation oncologists with diverse areas of expertise; biostatisticians; and pharmacists. As with the PRMC, members are invited by the Director of SCC to serve two-year terms, after which they may be reappointed for additional terms. A complete and current roster may be found on the QASMC website (https://siteman.wustl.edu/research/resources-for-researchers/quality-assurance-and-safety-monitoring/). While there may be minimal overlap, QASMC representation does not duplicate that of the PRMC and the same individual does not chair or have supervisory responsibility over both committees. The Clinical Protocol and Data Management leader does not chair and is not a member of the QASMC.

QASMC Review Process

The QASMC meets on a monthly basis to review quality assurance audits, unanticipated problems, and interim DSM/DSMB reports for all ongoing interventional investigator-initiated trials. QASMC may review other, non-investigator-initiated trials as determined at initial submission by the PRMC; most notably, these include multicenter trials where SCC is not the coordinating center but the coordinating center is unable to provide comprehensive DSMC oversight documentation.

Based upon information from the DSM/DSMB reports, annual audits, and/or unanticipated problem reviews, the QASMC will issue a recommendation regarding continuation of the study: either the study may continue with no modification or the study may continue after the QASMC, PRMC, and IRB review and approve a requested amendment.

QASMC Quorum Requirements

In order for a QASMC meeting to convene, quorum must be met. Quorum is defined as the faculty chair plus at least 50% of other committee members.

QASMC Assurance of Confidentiality during Review

In general, no communication, either written or oral, of the deliberations or recommendations of the committee will be made outside of the committee except as provided for in the QASMC policies and procedures. Each member of the QASMC must sign a statement of confidentiality.

QASMC Review for Progress and Safety of Participants – Audits

Audits are conducted for all investigator-initiated therapeutic trials and for non-therapeutic but interventional studies at the request of the QASMC or PRMC. Scheduling of an audit for a new study is triggered when the first patient is enrolled to the study in the SCC administrative CTMS. In some instances, the enrollment of the first patient may trigger an abbreviated audit to ensure the effectiveness of data collection tools, accuracy of data, and conduct in accordance with the protocol at the outset of the trial, with results communicated to the team.

For each audit, the audit team consists of a QA Advisor and a QA Auditor. QA Auditors conduct a systematic review of the study at the time of the audit by assessing the quality of trial execution and ensuring that the risks of the study, as reported by the research team, are not excessive. They also complete a direct comparison of recorded research data with the primary medical source documents in a random sample of cases and review compliance with regulatory requirements for the protection of human subjects and investigational drug accountability (if applicable).

Audits generally occur annually after triggered until the study closes to enrollment, but the QASMC may increase or decrease audit frequency or duration (e.g. through active treatment phase even after closure to enrollment) as needed. Common reasons for adjusting frequency include accrual rate (quickly or slowly accruing studies), risk level to patients (low risk), and substantive concerns raised during a prior audit.

A QA audit includes review of the following:

- data forms for accuracy and completeness
- participant eligibility
- outpatient and inpatient records to assess subject management
- regulatory maintenance, including acquisition of all appropriate PRMC and IRB approvals for study amendments and annual renewals
- adverse events and reporting
- informed consent documents and consent/re-consent process
- investigational drug logs (if applicable)

The number of cases selected for review is determined by enrollment to the study. For studies with 8 or fewer subjects, all subjects will typically be audited. For studies with more than 8 patients but fewer than 100 patients, a random sample of 5 to 10 subjects will be selected. For studies with more than 100 patients enrolled, 10% of patients will be selected (up to 25 subjects). For studies that are conducted at multiple institutions where SCC is the coordinating center, at least 1 patient (or 10% of patients, whichever is greater) will be selected from each participating institution.

At the conclusion of the QA audit, an audit report is prepared by the audit team and presented to the QASMC at its next scheduled meeting. The Committee will choose an initial recommendation from the following options:

1. Approved or approved with comments
2. Contingent approval
3. Deferred

In certain cases, the audit report will not be presented to the full committee but will instead be reviewed first by the QA Advisor. This will occur for audits that result in no findings or minor/low risk findings. The QA Advisor may at that time approve the audit, request information, make recommendations for improvement, or defer the report to the full convened committee meeting.

QASMC Committee Feedback and Follow-Up – Audits

Suggestions from all members of the committee are incorporated into the final report and the report is sent to the PI and key members of the study team. If a response is required from the PI, it is due within 30 days of the date of the letter and is reviewed by the QASMC Chair, who determines whether the audit can be approved, requires additional information, or must return to the full committee for further review. The PI response consists of a letter addressing each QASMC comment or recommendation with applicable documentation and revised materials attached. Given the importance of timely review, accrual will be suspended to those studies where the audit response is overdue by more than 120 days. In addition, for NCI-funded studies, QASMC can suspend studies if committee requirements are not met. In this instance, QASMC staff will communicate the suspension to the PI, IRB, and NCI Program Director for funding the trial.

At time of audit approval, the audit report, approval letter, and PI response letter (if applicable) are shared with the Washington University IRB and the Office of the Vice Chancellor for Research.

DSMB Requirements

In addition to regular QA audits, DSM/DSMB reports are prepared by the PI in accordance with the trial's DSM plan, and submitted to, reviewed by, and approved by QASMC. The Siteman Cancer Center independent standing DSMB must be utilized (or an *ad hoc* DSMB must be established) if the proposed study meets any of the following criteria:

- The study is a randomized phase III clinical trial
- The study is multi-institutional
- The study is determined to be a high-risk intervention
- The study includes a blinded treatment arm
- The study has a large expected accrual (n > 300)

The Siteman Cancer Center independent standing DSMB has a faculty chair and includes faculty representatives specializing in medical oncology, radiation oncology, surgical oncology, pediatric hematology/oncology, OB/GYN oncology, and biostatistics. At least two uninvolved faculty (may include the faculty chair) and one uninvolved statistician must be present for each meeting. Individuals are invited to join the SCC independent standing DSMB by the faculty chair.

Ad hoc DSMBs consist of at least two clinical investigators and one biostatistician. While there is a minimum of three members on a DSMB, more members may be included at the discretion of the study PI or as recommended by the QASMC, PRMC, or other regulatory body.

All members of the SCC independent standing DSMB and every *ad hoc* DSMB must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital, unless an external ad hoc member is necessary due to a conflict of interest. Members of a DSMB must not be investigators on the study for which they are providing monitoring services. They are subject to the Washington University policies regarding standards of conduct and conflicts of interest.

The DSMB must regularly review data relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, operating procedures, forms completion, intervention effects, accrual, and subject safety. The SCC independent standing DSMB meets every two months (with the frequency of review of any given study dictated by the study protocol), and *ad hoc* DSMBs must meet on a regular schedule as defined by the protocol.

The DSMB is expected to:

- Assess the trial's overall futility based on its design and objectives;
- Identify problems relating to patient safety over the course of the study;
- Identify any needs for additional data relevant to patient safety issues and request these data from the PI;
- Review SAEs and all other patient safety data to determine possible safety measures (pausing enrollment, revising consent form, etc.);
- Review formal interim analyses of the study's primary endpoint (if available);
- Review reports of related studies (to determine whether the monitored study needs to be changed or terminated);
- Review major proposed modifications to the study prior to their implementation; and
- Consider the rationale for continuation of the study and make a recommendation for or against continuation of the trial.

After review of the DSM report, a recommendation is made and voted on. Recommendations are:

- Continue accrual with no changes
- Continue accrual with changes
- Suspend accrual until changes are approved
- Close trial

- Report results
- Request additional information
- Continue monitoring per study requirements; further standing DSMB reports are not required

Meeting minutes are drafted in order to summarize the key points of discussion and debate, requests for additional information, response of the investigators to previous recommendations, and recommendations from the current meeting. If concerns are identified, the minutes will outline the concerns, the board's discussion of the concerns, and the basis for any recommendations the DSMB has made in response to the concerns.

The meeting outcome is communicated to the study PI, who is responsible for ensuring that the DSMB report and recommendation are communicated to QASMC and other participating institutions (if applicable). The meeting minutes are not transmitted directly to the study PI.

If the DSMB recommends that a study be changed or closed early for patient safety or efficacy reasons, the research team must act to implement the change as expeditiously as possible. In the event that the research team does not concur with the DSMB, then the QASMC Chair must be informed of the reason for disagreement. The research team, DSMB Chair, and QASMC Chair will be responsible for reaching a mutually acceptable decision about the study.

For studies where Washington University is the coordinating center and a DSMB is required because the study is multicenter, data and safety monitoring may be performed by QASMC until such a time as the study enrolls its first patient at another participating institution, at which point a DSMB is required thenceforth.

DSMB Assurance of Confidentiality during Review

In general, no communication, either written or oral, of the deliberations or recommendations of the board will be made outside of the committee except as provided for in the QASMC policies and procedures. Each member of the DSMB must sign a statement of confidentiality.

QASMC Review for Progress and Safety of Participants – DSM/DSMB Reports

A DSM/DSMB report contains the following information:

- Study demographic information (local protocol number, title, list of primary study team members, study sites, primary and secondary sponsors, phase, IND/IDE status, date of most recent QA audit, and study status and history (including activation and suspension dates)
- Accrual information, including study-wide target accrual and actual accrual, anticipated and/or actual accrual end date, and accrual by year by site (if applicable)
- Subject status information presented both in cumulative format (total number of subjects who consented, enrolled, screen failed, started intervention, discontinued intervention, went off study, expired) and current format (number of subjects in screening, on intervention, in follow-up, or off study at time of report)
- Protocol objectives and a list of participants who are evaluable for each objective
- History of study (including summaries of substantive amendments, accrual suspensions and reasons, protocol exceptions, errors, and breaches of confidentiality)
- Summary of exceptions, noncompliance reports, and unanticipated problems reported to the IRB
- Early stopping rules and data describing whether the stopping rules have been met (if applicable)
- Interim analysis plans and the results of interim analysis (if applicable)
- Separate SAE and worst grade toxicity tables, each separated by site (if applicable) and arm/cohort/dose level (if applicable)
- Participant-level response and survival data by arm/cohort/dose level (if applicable)
- Summary of specimen collection (percentage of participants who have had specimens collected at each required time point)
- Abstract submissions or publications

- Summary of recent literature that reports developments that may affect the safety of participants or the ethics of the study

The first DSM/DSMB report is required either 30 days after the enrollment of the fifth participant (if sooner than 6 months after study activation) or 6 months after study activation (provided at least one patient has been enrolled; if zero patients have been enrolled at the 6-month mark, the first report will be required one year after accrual opens provided at least one patient has been enrolled). The frequency of subsequent reports is dictated by the protocol, with the last report due 6 months after the last patient has completed treatment.

Accrual will be suspended to studies where the DSM/DSMB report is overdue by more than 120 days. A notice will be sent to the Washington University IRB, the PRMC, and the research team, as well as to the NCI Program Director responsible for funding the trials (if applicable). The Washington University IRB will notify the Office for Human Research Protections (OHRP) and FDA (if applicable) in accordance with the requirement that all suspensions and closures be reported to these agencies.

DSM/DSMB reports are assigned to a QA Advisor and are reviewed by the QASMC for severity and frequency of adverse events, accrual rate, SAEs, and the representation of risks in the informed consent document. The Committee will make one of the following decisions:

1. Approved or approved with comments
2. Contingent approval
3. Deferred

When a revision is requested, the research team is expected to revise the documents as required and include them with the response to QASMC. Given the importance of timely review, accrual will be suspended on those studies where a contingency or deferral response is overdue by more than 120 days, and a notice will be sent to the Washington University IRB, the PRMC, and the research team.

QASMC Adverse Event Review

Beyond the regular QA audits and DSM reports, unanticipated problems for investigator-initiated studies are reviewed weekly by the QASMC Chair as well as at monthly QASMC meetings. If needed, letters requesting clarification of an unanticipated problem are sent to the PI following the meeting.

QASMC Policies and Procedures

The QASMC's full policies and procedures document may be found in Appendix A.

Processes and Reporting Functions for Multicenter Trials Coordinated by Washington University

Regulatory Requirements

The Washington University principal investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites following Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs in a timely fashion. Upon obtaining local IRB approval, documentation of such shall be sent by the study team at a secondary site to the Washington University study team. Additionally, documentation of participating sites' IRB approvals of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be forwarded to the Washington University study team.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

Data and Safety Monitoring – QASMC Audits

Washington University (via the QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation, or permit auditor access to electronic medical records in accordance with their internal institutional policies. Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Participating sites are permitted to self-audit provided the frequency and scope of the audit is compatible with QASMC requirements and the site provides the full audit report to QASMC in a timely fashion. Approval of a request to self-audit is granted by the chair of the QASMC.

Data and Safety Monitoring – DSMB Review and Reports

Siteman Cancer Center independent standing DSMB will be utilized (or an *ad hoc* independent DSMB will be specifically convened) for multicenter trials coordinated by Washington University to review toxicity at least every 6 months following enrollment of the first patient at the first secondary site. DSMB requirements and reports are described above.

Adverse Event Reporting

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all protocol-defined reportable events within protocol-defined timeframes, followed by a formal written report.

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred within protocol-defined timeframes. This includes events that take place at Washington University and events that take place at other secondary sites, if applicable.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

Washington University Institutional Review Board (IRB)

The Washington University IRB (supported by the Human Research Protection Office (HRPO)) reviews all research involving human subjects at the Washington University Medical Center and its affiliated hospitals. The IRB ensures that research meets ethical standards and is conducted in accordance with federal, state, and local regulations. The initial review of a cancer-related trial by the IRB can only take place after PRMC review and approval. As part of the annual review process, the IRB examines trials for accrual and reviews study progress.

The IRB reviews Unanticipated Problems and Reportable Events as they are received and reviews aggregate adverse event reports annually.

All prospective changes to a study protocol must be reviewed and approved by the IRB prior to implementation, except in rare cases in which a change must be made to mitigate risk to a subject.

Disease- or Discipline-Focused Groups (Research Focus Groups)

Part of the initial submission package includes study prioritization and approval by the appropriate Research Focus Group leader. Studies are prioritized as follows:

- Investigator-initiated local studies (with or without external sponsorship), and cooperative group studies for which an SCC member is the national PI
- Cooperative group studies or other NCI-approved multicenter studies
- Industry-initiated studies

Within these larger categories of studies, the Research Focus Group ranks studies by evaluating the scientific novelty and merit of the study, the patient population targeted by the study vis-à-vis the population found in SCC's catchment area, and the number of competing or overlapping trials for the proposed patient population. Authority for final prioritization rests with the PRMC, which can accept, query, or decline the initial prioritization by the Research Focus Groups.

Program for the Elimination of Cancer Disparities (PECaD)

Ensuring appropriate representation by gender, race, and ethnicity in cancer clinical trials is mandated by the NCI: all research with human subjects must include adequate numbers of women and minorities to allow for valid analyses of differences in the interventional effect; recruitment must be conducted so that no group is unduly burdened and that no group is unduly benefited; and any research proposal must describe the proposed study population in terms of gender and race/ethnicity as well as the rationale for inclusion.

The Program for the Elimination of Cancer Disparities (PECaD) monitors research accrual and supports investigators in their efforts to achieve appropriate representation. A PECaD representative is present at PRMC meetings when needed to ensure communication about specific trials. The standard for evaluation of "appropriate representation" is determined by the patient population at SCC for that study's inclusion criteria. When protocols are submitted to the PRMC for annual renewal, the PECaD Clinical Studies Outreach team reviews aggregate accrual data by gender and race in order to compare the study's accrual to the overall incidence of eligible participants seen at SCC.

As a part of this process, PECaD offers guidance and links investigators to appropriate internal and community resources. If a study has continued problems reaching proportional accrual, and if the PI does not demonstrate efforts to improve minority accrual, PECaD may return the protocol to the full PRMC for discussion. The PRMC may then require other remedial steps from the PI. Also, for very flagrant violations, the PRMC can immediately suspend or close a study after discussion between PECaD and PRMC co-chairs.

Event Reporting

The PI is required to notify the Washington University IRB promptly of the following events:

- Unanticipated problems involving risks to participants or others
- Noncompliance with federal regulations or the requirements or determinations of the IRB

- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study

These events are reported to the IRB as per IRB policy. Definitions of each and the associated reporting requirements may be found in the IRB's policy document located on the IRB website, https://hrpo.wustl.edu/research-toolkit/policies/.

For multicenter trials where WU is the coordinating center, WU investigators are responsible for ensuring events are reported appropriately to the Washington University IRB, QASMC, and other regulatory bodies as required by the study protocol. As coordinating center, WU is responsible for communicating adverse events to participating institutions, which are then responsible for regulatory reporting requirements as determined by their local institution.

Reporting to NCI Program Director

Given the importance of timely review, accrual will be suspended to those studies where an audit response or DSM/DSMB report is overdue by more than 120 days. A notice will be sent to the Washington University IRB, the PRMC, and the research team, as well as to the NCI Program Director responsible for funding the trials (if applicable). The Washington University IRB will notify the Office for Human Research Protections (OHRP) and FDA (if applicable) in accordance with the requirement that all suspensions and closures be reported to these agencies.

Investigator Requirements and Responsibilities

The PI of each study is responsible for the design, conduct, and final analysis of their protocol. It is the expectation that the study PI is monitoring data and safety continuously throughout the conduct of the study.

Conflict of Interest

Members of the SCC study team are expected to disclose relevant conflicts of interest per WU policy. Disclosures are made through the WU Research Gateway. All university faculty as well as any individuals who are independently responsible for the design, conduct, or reporting of research at WU are required to complete a financial disclosure statement that identifies all research in which the individual is engaged at the time of the disclosure and discloses all personal financial interests and those of their family (regardless of value) that appear to be related to the individual's institutional responsibilities. Disclosures are required at minimum annually but may also be required at the time of submitting a research proposal or when personal financial interests change in a manner that is relevant.

For purposes of WU policy, a financial conflict of interest refers to situations in which it is reasonably determined that a material financial interest could directly and significantly affect the design, conduct, or reporting of research. The Conflicts of Interest Review Committee (CIRC) evaluates individuals' personal financial interests and assesses relatedness and risk in determining whether a conflict of interest exists and, when applicable, in determining the appropriate management plan. More details can be found on the CIRC website (https://research.wustl.edu/topics/conflicts-of-interest/).

Conflicts of interest can also include professional interest in additional to financial conflicts of interest. Conflicts of interest must be disclosed to the relevant committee (PRMC, QASMC, DSMB) at the start of service or as they develop during a member's tenure on the committee. Decisions concerning whether individuals with potential

conflicts of interest or the appearance of conflicts of interest may participate in a particular committee will be made by the committee in accordance with institutional policies. Committee members with a conflict of interest are not permitted to vote on committee decisions regarding the studies for which they have conflicts.

Appendix A: Quality Assurance and Safety Monitoring Committee (QASMC) Policies and Procedures

These policies and procedures were refreshed in July 2023.

The Quality Assurance and Safety Monitoring Committee (QASMC)

To maintain National Cancer Institute (NCI) designation, the Alvin J. Siteman Cancer Center (SCC) must ensure that research data generated under its sponsorship are of high quality, reliable, verifiable, and reproducible. Quality assurance auditing was implemented in November 1997 by the Quality Assurance Subcommittee (QAS) of the Protocol Review and Monitoring Committee (PRMC). Standards introduced in 2001 by the NCI for data and safety monitoring led to the formation of a Quality Assurance and Data Safety Monitoring Committee (QASMC) in September 2001 to replace the QAS. The QASMC serves as the SCC's Data and Safety Monitoring Committee (DSMC).

Members of the QASMC are appointed by the Director of the SCC and are asked to serve for two years. Appointments may be renewed for additional terms. Members are selected based on the experience they have in designing or conducting clinical trials or special clinical expertise (pharmacology). See https://siteman.wustl.edu/research/clinical-research-resources/quality-assurance-and-safety-monitoring/ for the current membership of the Siteman Cancer Center QASMC.

QASMC members are subject to the Washington University Medical School and Siteman Cancer Center policies regarding standards of conduct. Individuals invited to serve on the QASMC will disclose any potential conflicts of interest, whether real or perceived, to the QASMC Chair and the appropriate Siteman Cancer Center official(s), in accordance with the institution's policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94. Potential conflicts that develop during a member's tenure on the QASMC must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in the QASMC will be made in accordance with the institution's policies. During meetings, QASMC committee members who are PI of the study team being discussed must leave the room during voting. QASMC committee members who are engaged research team members of a study being reviewed must not be assigned as the QA Advisor for that study.

Goals and Responsibilities of the QASMC

In compliance with the NCI-approved Institutional Data and Safety Monitoring (DSM) Plan, implemented in August 2001, and most recently updated October 2020, the QASMC is charged with overseeing the data and safety monitoring of investigator-initiated trials, reviewing all serious adverse events (SAEs) that occur on investigator-initiated interventional trials conducted under the auspices of Siteman Cancer Center (SCC), and reviewing quality assurance (QA) audits on investigator-initiated therapeutic trials, as well as any other trial at the request of the PRMC. Additional audits may be conducted at the request of the PI, if resources are available.

Specific Responsibilities of the QASMC

- Reviewing routine data and safety monitoring (DSM) reports, which are typically submitted semi-annually
- Arranging for QA Advisors from its roster to provide expertise for QA audits
- Performing QA audits
- Assessing the trial audit findings of investigator-initiated therapeutic trials (and others audited at the

request of the PRMC) performed by the QA Auditors and Advisors
- Making recommendations to the study team based on the audit findings
- Reviewing all Unanticipated Problems occurring on investigator-initiated interventional trials at SCC

Documentation of SAE reports, DSM/DSMB reports, and QA audits is maintained in separate files from the PRMC documentation. PRMC files are marked to indicate the existence of a QASMC file. Tracking forms are completed to indicate the status of reports and, when final, the tracking forms are put on record in the PRMC file. The approved QASMC meeting minutes are submitted to PRMC leadership.

QASMC Meetings

The QASMC meets on a monthly basis to review QA audit reports, unanticipated problems, and interim DSM/DSMB reports for all ongoing interventional investigator-initiated trials.

In general, no communication, either written or oral, of the deliberations or recommendations of the committee will be made outside of the committee except as provided for in this document. Each member of the QASMC must sign a statement of confidentiality.

QASMC Policies and Procedures: Unanticipated Problems (UPs) – Adverse Events (AEs)

UP (AEs) Reporting Requirements

Unanticipated problem (UP) adverse event reports are submitted to the Washington University Human Research Protections Office Committee (HRPO) [the institutional review board]. QASMC receives Unanticipated Problem reports on cancer-related investigator-initiated protocols electronically from the protocol-specific research team(s) at the time of acknowledgement of the event by the IRB. The definitions of reportable events are provided in the HRPO policies and procedures.

UP adverse event reports should contain, at a minimum, the following information:

- NCI Common Toxicity Criteria (CTC) description of the event
- NCI CTC grade of the event
- Start date of the UP
- Stop date of the UP
- Outcome
- Relevant laboratory and diagnostic test results, including dates
- Start date of protocol intervention and/or therapy, including cycle information (if applicable)
- Last date of protocol intervention and/or therapy (immediately prior to UP)
- Relationship of event to investigational drugs or intervention (approved by the Principal Investigator)

The reportable adverse event case report forms specified in the protocol should be utilized for QASMC reporting. It is critical that the reportable adverse event form be reviewed, signed, and dated by the Washington University PI prior to submission.

UP Report Submissions

An electronic copy of the reportable event must be submitted to QASMC at qasmc@wustl.edu. Please note: All reportable UPs should be submitted to the HRPO per their policies, procedures, and/or recommendations as a separate submission.

UP Review Procedures

UP reports are reviewed during the QASM team's weekly meetings with the QASMC chair. The event is assessed for accuracy of the reporting and attribution. The chair assesses the progress of the study and the progress of the participants to determine if protocol modifications are necessary. This includes reviewing the consent form to ensure that, if appropriate, the risk of the event is adequately addressed. The chair will decide whether to approve an event or present it to the Committee for discussion.

After full-committee discussion (if required), one of the following decisions is documented and communicated to the study team:

1. **Approved –** No further action required.
2. **Approved with Comments -** Educational letter to be sent to the research team. Information is provided to improve future reporting but does not require a re-submission or revision at this time. (e.g. protocols that are in follow-up only and/or administrative issues).
3. **Correction Required –** Letter to be sent to the research team documenting the Committee's decision that a revision to the event submission and/or the protocol/consent is to be made or that additional information is needed prior to approving the report. When a revision is requested, the research team should submit the revisions within 30 days.

QASMC Policies and Procedures: Data and Safety Monitoring (DSM) Reports

DSM Reporting Requirements

In compliance with the Institutional DSM Plan, the QASMC requires DSM/DSMB reports to be submitted on institutional trials as designated by PRMC. A notification that the DSM/DSMB report is due will be sent to the research team approximately 30 days before the due date.

The first DSM/DSMB report is required either 30 days after the enrollment of the fifth participant (if sooner than 6 months after study activation) or 6 months after study activation (provided at least one patient has been enrolled; if zero patients have been enrolled at the 6-month mark, the first report will be required one year after accrual opens provided at least one patient has been enrolled). The frequency of subsequent reports is dictated by the protocol, with the last report due 6 months after the last patient has completed treatment.

If there is more than one clinical site, the study principal investigator is responsible for sending the reports to individual site principal investigators, who in turn are required to distribute the report to their local IRBs, as detailed in the NIH "Guidance on Reporting Adverse Events to Institutional Review Committees for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999).

Given the importance of timely review, **accrual will be suspended** to those studies where the DSM/DSMB report is overdue by more than 120 days. Reminders and requests for information are sent regularly after the due date. If the report is not received within 120 days of its due date, a notice will be sent to the Washington University IRB, the PRMC, and the research team, as well as to the NCI Program Director responsible for funding the trials (if applicable). The Washington University IRB will notify the OHRP and FDA (if applicable) in accordance with the requirement that all suspensions and closures be reported to these agencies. Once the DSM/DSMB report is received and approved by the QASMC, notice will be sent to resume the study.

DSM Documentation

Single Institution Studies

Reports should be prepared by the research team or DSMB and signed and dated by the PI or Chair of the Committee, as applicable. **All relevant information should be provided** but at a minimum, reports must include the following items:

- Study demographic information (local protocol number, title, list of primary study team members, study sites, primary and secondary sponsors, phase, IND/IDE status, date of most recent QA audit, and study status and history (including activation and suspension dates)
- Accrual information, including study-wide target accrual and actual accrual, anticipated and/or actual accrual end date, and accrual by year by site (if applicable)
- Subject status information presented both in cumulative format (total number of subjects who consented, enrolled, screen failed, started intervention, discontinued intervention, went off study, expired) and current format (number of subjects in screening, on intervention, in follow-up, or off study at time of report)
- Protocol objectives and a list of participants who are evaluable for each objective
- History of study (including summaries of substantive amendments, accrual suspensions and reasons, protocol exceptions, errors, and breaches of confidentiality)
- Summary of exceptions, noncompliance reports, and unanticipated problems reported to the IRB
- Early stopping rules and data describing whether the stopping rules have been met (if applicable)
- Interim analysis plans and the results of interim analysis (if applicable)
- Separate SAE and worst grade toxicity tables, each separated by site (if applicable) and arm/cohort/dose level (if applicable)
- Participant-level response and survival data by arm/cohort/dose level (if applicable)
- Summary of specimen collection (percentage of participants who have had specimens collected at each required time point)
- Abstract submissions or publications
- Summary of recent literature that reports developments that may affect the safety of participants or the ethics of the study

Multi-site Institution Studies where WU is the coordinating center

Reports should include all relevant information as detailed above, incorporating data from all study sites.

Multi-site Institution Studies where WU is not the coordinating center

The coordinating site must provide a study summary at a minimum of once per year. This report should include information regarding accrual, toxicity and response (where appropriate) from all participating sites.

Studies requiring a Data and Safety Monitoring Board (DSMB)

DSMB Documentation should include:

- DSM report (as prepared by the research team and described above)
- Recommendation report from DSMB (prepared and signed by DSMB chair)
- Current consent

- SAE summary

DSM/DSMB Report Review Procedures

Requests for and receipt of DSM/DSMB reports are logged into the SCC CTMS. DSM/DSMB reports submitted to the QASMC office will be pre-reviewed by a QA Auditor and then scheduled for review at the next monthly QASMC meeting. DSM reports are assigned to a primary faculty advisor and reviewed for severity and frequency of adverse events, accrual rate, reporting of SAEs to HRPO and the representation of risks in the consent.

After full-committee discussion, the Committee will make one of the following decisions:

- **Approved** – no further action required.
- **Approved with Comments** – a letter will be sent to the research team or DSM Committee
- **Contingent Approval** – minor modifications requested; a written response is required from the PI that will be reviewed by the QASMC chair.
- **Deferred** – Committee has concerns that require a written response from the PI to be reviewed by the full Committee.

When a revision is requested, the research team should prepare the appropriate IRB-required documents and include these with the response to QASMC. Once the revisions are reviewed by QASMC, the study team will submit to PRMC and the IRB as necessary. In all cases, a copy of the final report and approval letter will be forwarded to the research team.

DSMB Membership

A DSMB will consist of at least two clinical investigators and one biostatistician. While there is a minimum of three members on a DSMB, more members may be included at the discretion of the study PI or as recommended by the QASMC, PRMC, or other regulatory body. All members of a DSMB must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital unless an external ad hoc member is necessary due to a conflict of interest. Members of a DSMB must not be investigators on the study for which they are providing monitoring services. They are subject to the Washington University Medical School policies regarding standards of conduct. Individuals invited to serve on a DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

Siteman Cancer Center has a standing independent DSMB. Please refer to the SCC standing independent DSMB policy and procedure document for information specific to that board. It meets all guidelines set forth for *ad hoc* DSMBs as described in this document and the institutional data and safety monitoring plan.

DSMB Responsibilities

The DSMB must regularly review data relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trials operating procedures, form completion, intervention effects, accrual, and subject safety. Specifically, the DSMB is expected to:

- Assess the trial's overall futility based on its design and objectives;
- Identify problems relating to patient safety over the course of the study;
- Identify needs for additional data relevant to safety issues and request these data from the PI;
- Review SAEs and all other patient safety data to determine possible safety measures (pausing

enrollment, revising consent forms, etc.);

- Review formal interim analyses of the study's primary endpoint (if available);
- Review reports of related studies (to determine whether the monitored study needs to be changed or terminated);
- Review major proposed modifications to the study prior to their implementation; and
- Consider the rationale for continuation of the study and make a recommendation for or against continuation of the trial.

DSMB Meetings

The agenda for DSMB meetings may be drafted by the member of the study team coordinating the DSM report. The agenda and meeting materials (including the DSM report) must be submitted to DSMB members with enough time to allow sufficient review to occur prior to the meeting.

Before each meeting, when the agenda is sent out, the meeting coordinator will ask all DSMB members to state whether they have developed any new conflicts of interest since the last meeting. If a new conflict is reported, the other members of the committee will determine if the conflict limits the ability of the DSMB member to participate in the discussion and whether the member needs to be replaced on the board.

The DSMB will review the DSM report (as detailed above) as well as formal interim analyses of the primary endpoint if available, reports of related studies (to determine whether the monitored study needs to be changed or terminated), and major proposed modifications to the study prior to their implementation.

The DSMB is expected to identify problems relating to safety over the course of the study, including identifying any needs for additional data relevant to safety issues and requesting these data from the study investigators. At their meeting, they will consider the rationale for continuation of the study and make a recommendation for or against continuation of the trial.

It is expected that all DSMB members will attend every meeting (in person or remotely). However, quorum for voting is half the standing members plus one (for boards with 4 or more members) or 2 members (for boards with 3 members).

It is permissible for the study PI to attend the DSMB meeting, but s/he must not be present for voting.

DSMB Recommendations

DSMB recommendations should be based on results for the trial being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the research team to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

After review of the DSMB report, a recommendation will be made and voted on. Recommendations are:

- continue accrual with no changes
- continue accrual with changes
- suspend accrual until changes are approved
- close trial
- report results
- request additional information
- continue monitoring per study requirements; further standing DSMB reports are not required

Meeting minutes will be drafted in order to summarize the key points of discussion and debate, requests for additional information, response of the investigators to previous recommendations, and recommendations from the current meeting. If concerns are identified, the minutes will outline the concerns, the board's discussion of the concerns, and the basis for any recommendations the DSMB has made in response to the concerns.

The meeting outcome will be communicated to the study PI, who is responsible for ensuring that the DSM report and DSMB recommendation are communicated to QASMC, the IRB, and other participating institutions (if applicable). The meeting minutes will not be transmitted directly to the study PI.

If the DSMB recommends that a study be changed or closed for patient safety or efficacy reasons, the research team must act to implement the change as expeditiously as possible. In the event that the research team does not concur with the DSMB, then the QASMC chair must be informed of the reason for disagreement. The research team, DSMB Chair, and the QASMC Chair will be responsible for reaching a mutually acceptable decision about the study.

Release of Outcome Data

It is not recommended that outcome data be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment.

The DSMB may approve the release of outcome data on a confidential basis to the trial PI for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials.

Any release of outcome data prior to the DSMB recommendation for general dissemination of results must be reviewed and approved by the DSMB.

Confidentiality Procedures

In general, no communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided for in this policy. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

Conflict of Interest

A financial conflict of interest refers to a situation in which it is reasonably determined that a material financial interest could directly and significantly affect the design, conduct, or reporting of research. (https://research.wustl.edu/determining-and-managing-research-fcois-procedures/) Individuals invited to serve on the DSMB will disclose any potential conflicts of interest, whether real or perceived, to the trial principal investigator and the appropriate institutional official(s), in accordance with the institution's policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest. Potential conflicts that develop during a member's tenure on a DSMB must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSMB will be made in accordance with the institution's policies.

QASMC Policies and Procedures: Quality Assurance (QA) Audits

Types of Quality Assurance

Two distinct types of monitoring are performed. The first is provided by the PRMC. All cancer-related studies are initially reviewed for scientific merit. Subsequently, the PRMC reviews the overall progress of each study to assure that the projected accrual goals are being met, and that over-accrual is avoided. The PRMC Policies and Procedures are available on the PRMC website at: https://siteman.wustl.edu/research/resources-for-researchers/protocol-review-and-monitoring-committee/.

The second type of monitoring is provided by the QASMC. It reviews the quality of trial execution and ensures that the risks of the study, as reported by the research team, are not excessive. Through direct comparison of the recorded research data with the primary medical record in a random sample of cases, this review process enhances the delivery of accurate and reliable research trial data and results for data analysis. At the same time, compliance with regulatory requirements for the protection of human subjects and investigational drug accountability (if applicable) will be checked. Additionally, the QASMC review process provides educational support to SCC members conducting cancer research regarding issues related to data quality, data management and other aspects of cancer research quality assurance.

Protocol Selection and Notification of Audit

The QASMC audits all institutional therapeutic trials, as well as other research trials (e.g., diagnostic trials) as designated by the PRMC. The PRMC decides, generally at the time of approval, which institutional non-therapeutic research trials will be audited by the QASMC. The QASMC will also consider auditing other trials if requested by a PI, for example, as an interim cooperative group trial review. If Washington University is the coordinating center, each site will be audited by Siteman Cancer Center personnel, unless the outside institution has an auditing mechanism in place and can provide a report. The audit by SCC personnel will take place at the outside institution if there are funds in place (responsibility of the PI). If there are no funds for travel, the auditor's schedule does not allow for travel, or there are fewer than five subjects at a site, the outside sites will be asked to send copies of all audit materials. If Washington University is the coordinating center and the audit of the outside sites will occur at SCC, the audit notification will be sent to the SCC Research Coordinator, and it is the responsibility of the Research Coordinator to obtain audit materials in this situation. If there are funds for travel, the SCC Research Coordinator will assist in contacting and planning the audit with the outside institution. Notification of an upcoming audit will be sent to the research team approximately 6 weeks ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Case Selection

Generally, a minimum number of cases equivalent to at least 10% of the subjects accrued to the study will be reviewed. The number of cases selected for review will be determined as follows:

- All cases if current enrollment is ≤ 8;
- 5-10 cases if the number enrolled is 9-100;
- 10% of cases if the number enrolled is > 100 (up to a maximum of 50 cases)
- For studies with greater than 10 patients, the cases should be randomly selected, but divided 2:8 between those enrolled prior to and since the last audit so that the sample is representative

of the full spectrum of the enrollment period. In the case of studies that enroll donors (e.g., bone marrow transplant studies), 3 donor/recipient sets will also be randomly selected and reviewed. For studies qualifying for abbreviated audits (per the risk-based auditing guidelines described in section 6.5), a total of 5 cases will be selected if the number enrolled is ≤100.

Multi-Institutional Trials

For sites with 5 or more patients, the case selection process is identical to the above section.

The patient lists for all sites with fewer than 5 patients will be condensed to one list and the cases will be selected using the above process.

Audit Frequency

The first audit of a study should occur approximately 6 months after the first subject is enrolled, but may be earlier or later depending on accrual goals and actual recruitment. If no subjects have been enrolled 12 months after a study opens to accrual, the QASMC will defer the study to PRMC. Subsequent audits are to occur at a frequency specified by the QASMC during recommendation deliberation for each audit report. Typically, studies are re-audited annually, but a study may be audited biennially, semi-annually, or after 3 months (e.g., for cause, or accrual driven). The QASMC may use its discretion to waive or postpone an audit for small non-therapeutic studies with very low risk (e.g., auditor workload). Studies will not be re-audited until at least 2 new patients have been enrolled since the prior audit.

Risk-Based Auditing

Because the types of studies audited vary widely, a risk-based approach to auditing has been adopted in order to balance the level of review and the level of risk associated with a given study (See Appendix B). Risk-based auditing guidelines are used to identify studies that qualify for abbreviated review at the time of subsequent audit. For abbreviated audits, 5 cases are selected for review if the total enrolled is <100. All 5 cases selected for abbreviated audit will have been enrolled since the prior audit. If <5 patients have been enrolled since the prior audit, all 5 cases selected for abbreviated audit should be previously unaudited, if possible.

Low Accrual

At the time that a study is due for audit, total subject accrual will be checked for accuracy and completeness and compared with the SCC Registry. If accrual is slower than projected, the research team will be put on alert that future renewals may be jeopardized if accrual is not improved in the interim.

QA and Committee Procedures

In preparation for the audit, a QA Advisor is assigned and the protocol is reviewed with the QA Specialist. In general, the QA Specialist will conduct the initial record review. A meaningful and random sample of clinical records, radiologic studies and other diagnostic data, pathology and cytochemistry reports, operative reports, laboratory data, HRPO reviews and consents, and investigational drug logs (if applicable) are examined to ensure that data management practices in the SCC adhere to protocol guidelines, that submitted information is accurate and complete, and that all federal human subjects regulations and NCI guidelines for investigational drugs have been followed. At the conclusion of the audit, the QA Specialist will discuss the findings with the QA Advisor and, as needed, with the research team to obtain clarification of apparent deficiencies. Following the QA audit, a report is drafted. The findings are presented at the following month's QASMC meeting for discussion and recommendations. After the meeting, the QA Specialist revises the draft report and sends the final report and cover letter

to the research team. If a written response from the PI is required, it is due in the Protocol Office within 30 days of the date of the letter.

Administrative Review

In certain cases, the audit report will not be presented to the full committee but will instead be reviewed first by the QA Advisor. This will occur for audits that result in no findings or minor/low risk findings. The QA Advisor may at that time approve the audit, request information, make recommendations for improvement, or defer the report to the full convened committee meeting.

Discussion of Protocol Problems

It is important to note that an inclusive and precise definition of what constitutes unacceptable audit findings is difficult to construct. Rather than trying to develop an inclusive quantitative definition, the QASMC will attempt to use a common set of problems that will result in a request to the research team for further assessment. Examples include the following:

- Lack of annual HRPO and/or PRMC reviews for protocol;
- Lack of semi-annual DSM reports;
- Major addenda not reviewed on a timely basis or not submitted to HRPO;
- Subject entered prior to HRPO approval;
- Consent not obtained or consent form not current;
- Subject does not meet eligibility;
- Pre-treatment tests of major importance not performed;
- Data forms do not reflect medical records;
- Incorrect treatment given, wrong dose (>10%) given, wrong timing with no reason or explanation, failure to modify doses according to protocol, wrong route of administration, failure to document drug administration, or error in concomitant medications;
- Failure to obtain the required protocol baseline studies to effectively assess toxicity;
- Repetitive failure to get the necessary follow-up studies to measure toxicity;
- Failure to characterize toxicity or grade;
- Not reporting Grade 4 drug toxicity, not filing required Serious Adverse Event Reports with the HRPO, or not reporting treatment-related deaths to the HRPO;
- Failure to assess disease status according to the protocol guidelines.

The QA Specialist shall copy any managers of clinical areas that are involved in unacceptable audit findings on the final audit report (i.e. pharmacy, nursing, in-patient floors, infusion staff, etc.). It is the responsibility of the research team to ensure that the appropriate clinical managers address these findings involving their staff.

Evaluation of QA Findings

The assigned QA Advisor presents the audit assessment at the QASMC monthly meeting. The Committee then chooses an initial recommendation from the following options:

1. **Approved or approved with comments.** No deviations were discerned and no response from the research team is needed.
2. **Contingent.** Minor issues were raised by the audit. A written response is required from the PI that will be reviewed by the QASMC chair.
3. **Deferred.** Serious issues were raised in the audit, which require further input from the

PI. The full Committee will review the written response from the PI.

When a revision is requested, the research team should prepare the appropriate IRB-required documents and include these with the response to QASMC. Once the revisions are reviewed by QASMC, the IRB submission will be forwarded to PRMC for further processing.

Given the importance of timely review, accrual will be suspended on those studies where the response to the audit is overdue by more than 120 days. A reminder is sent approximately 30 days after the due date. If a response is not received in the Protocol Office within 90 days of its due date, a final reminder will be sent via email. If the response is not received within the next 30 days, a notice will be sent to the HRPO, PRMC, the research team, and the NCI Program Director responsible for funding the trials stating that accrual is suspended until further notice from the QASMC. HRPO will notify the OHRP and FDA (as applicable) in accordance with the requirement that all suspensions and closures be reported to these agencies. Once the response is received and approved by the QASMC, notice will be sent to resume the study.

Evaluation of PI Response

The chair or Committee will review the response, as described above and select one of the following decisions:

1. **Approved-** Response Acceptable
2. **Approved with Comments –** Minor issue(s) to be addressed in a letter.
3. **Contingent Approval –** Minor Issue(s) to be addressed and response to be reviewed by Chair**.**
4. **Deferred** – Serious issue(s) unresolved; response to be reviewed by Committee
5. **Disapproved –** Recommendation of PRMC to close study.

If the decision is made to approve the study for continuation, the PRMC will be notified via the QASMC meeting minutes. If the audit response receives contingent approval or is deferred, the PI will be required to provide an additional written response and the review process will be repeated until a decision by the QASMC is made to either approve or disapprove. When a decision is made to disapprove the study the findings will be submitted to the PRMC for review and discussion by the full Committee.

Preparation for QA audit

Research Team Responsibilities

The research team will need to prepare for the QA review by gathering **all source documentation** pertaining to the selected cases. For multi-modality studies, documentation from all modalities must be made available. These items should include:

- Hospital and/or outpatient charts (as relevant to the trial);
- Imaging reports, laboratory results and other special studies as required by the protocol (if not in patient chart);
- Operative, pathology and radiotherapy reports (if not in patient chart);
- Original signed and dated consent form for each patient (copy if original is not available);
- Completed data collection forms or access to database if entered electronically.
- The HRPO initial, renewal and amendment approvals
- Annual reports submitted to the HRPO
- All versions of the protocol and consent forms since initial HRPO approval

- Records regarding the disposition of investigational drugs, when applicable, specifically copies of drug orders, return receipts and NCI Drug Accountability Records

In addition to providing the above, it is recommended that the research team flag the charts to indicate eligibility documentation, pre-treatment requirements, treatment cycles, study tests, etc. in order to expedite the QA review procedure.

Day of QA Review

If requested, the research team will make conference room arrangements. The PI and research coordinator responsible for the study being audited are not required to be present at the review. However, the QASMC recommends that the research coordinator in particular be on-site in the event there are questions.

DSM Plan Summary

The cooperative groups have appropriate data and safety monitoring plans for all protocols and site-specific institutional plans are not needed. In addition, given the stringent FDA reporting guidelines, most pharmaceutical companies have DSM plans in place. It remains the responsibility of the institutional principal investigator to confirm that the DSM plan is outlined in an industry-sponsored protocol, or to obtain a description of the sponsor's plan (Standard Operating Plans) for submission of the protocol to the SCC Protocol Review and Monitoring Committee (PRMC).

In an effort to insure that all protocols have a DSM plan, the plan should be included in a separate section of the protocol and referenced in the protocol index. All DSM plans must include an assurance that summary reports will be provided to the QASMC on a regular basis. Templates for these reports are provided on the QASMC website:
https://siteman.wustl.edu/research/resources-for-researchers/quality-assurance-and-safety-monitoring/.

Guidelines for Data and Safety Monitoring Plans

1. NIH requires a data and safety monitoring plan (DSMP) for all clinical trials.
   - Observational studies and those that do not test interventions are not clinical trials.
   - Studies involving molecular or imaging tests are considered clinical trials only if the information from the diagnostic test may affect the outcome of study subjects or if the test itself imposes a risk to the study subject.
2. For ease of documenting compliance, the DSM plan should be described in a separate section of the protocol and referenced in the protocol index (sample plans provided below).
3. Essential elements of a DSM plan
   - Describe who will monitor the data and how frequently.
   - Describe the mechanism for evaluating and reporting adverse events, including which agencies will receive reports. All reports must go to the HRPO and the QASM Committee. In addition, depending on the study, reports may need to go to the study sponsor and/or the FDA.
   - Indicate how often reports will be provided to the QASMC.
   - Multi-institutional trials must identify who will be preparing and distributing timely summary reports of adverse events to all involved institutions.
4. Data and Safety Monitoring Boards
   - The need to have a DSMB for trials other than Phase III studies is at the investigators'/institutions' discretion. ["Nor does NIH/NCI policy require that formal DSMCs be constituted for clinical trials other than Phase III, though investigators or institutions may wish to do so for certain non-Phase III trials involving particular risk, complexity, likely decisions about early stopping, or the need to obviate conflict of interest."]

- As regards the "discretionary" formation of DSMBs, the current NCI- approved SCC institutional DSM plan states that in addition to Phase III studies, a DSMB will be established if the trial
    a. is multi-institutional (see below)
    b. involves a high-risk intervention (gene therapy, cancer vaccine)
    c. has a blinded treatment arm
    d. has large expected accrual (n>300)
- Based upon on-going discussions with NCI, it is apparent that, despite our institutional plan, we have some "latitude" in allowing participation of our investigators in multi-institutional studies initiated at other sites, even if that site does not require a DSMB. This would apply especially to Phase II studies testing drugs for which there is already significant toxicity information (e.g., a Phase II study of an FDA-approved drug for a non FDA-approved indication). However, it is imperative that an adequate mechanism be in place for monitoring the protocol and reporting adverse events to all involved investigators.

5. Data and Safety Monitoring Reports for Institutional Studies
    - Semi-annual report to QASM Committee for review
    - Report prepared by investigator for Phase I-II, by DSMB for Phase III
    - Information to include in report
        a. Number pts enrolled/treated
        b. Summary of all adverse events (regardless of grade/attribution)
        c. Response evaluation (Phase II only)
        d. Summary of any recent literature reporting developments that may affect safety or ethics of study.

Sample Wording of DSM Plans for Investigator-Initiated Trials

Phase I Studies

The principal investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the QASM Committee. This report will include

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments, summary of accrual suspensions including start/stop dates and reason, and summary of protocol exceptions, errors, or breaches of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in Year 1, Year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study.

The study principal investigator and clinical research associate will monitor for serious toxicities on an ongoing basis. Once the principal investigator or clinical research associate becomes aware of an

adverse event, the AE will be reported to the HRPO and QASM Committee [*add other reporting requirements here if applicable*, *e.g. sponsor, FDA, collaborating institutions*] according to institutional guidelines.

For multi-institutional Phase I studies consider an additional paragraph

To insure safe dose-escalation, all sites will be required to submit complete data to the principal investigator at the end of each course of treatment. Serious adverse events occurring at all sites will be reported to the principal investigator within 24 hours. The principal investigator will distribute SAE reports to all participating sites within 15 days of becoming aware of the event. The principal investigator will review data from all sites monthly. The semi-annual DSM reports will be distributed to the responsible investigator at each participating institution.

Phase II Studies

The principal investigator will review all patient data at least every six months, and provide a semi-annual report to the QASM Committee. This report will include

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments, summary of accrual suspensions including start/stop dates and reason, and summary of protocol exceptions, errors, or breaches of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in Year 1, Year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study.

The study principal investigator and clinical research associate will monitor for serious toxicities on an ongoing basis. Once the principal investigator or clinical research associate becomes aware of an serious adverse event, the SAE will be reported to the HRPO and QASM Committee [*add other reporting requirements here if applicable*, *e.g. sponsor, FDA, collaborating institutions*] according to institutional guidelines.

Phase III Studies, Multicenter Studies, High-Risk Studies, or Other Studies with a DSMB

An independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or

appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

Until such a time as the first secondary site enrolls its first patient, a semi-annual DSM report to be prepared by the study team will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after study activation at Washington University (if at least one patient has been enrolled) or one year after study activation (if no patients have been enrolled at the six-month mark).

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the QASM Committee. The DSMB must meet at least every six months beginning six months after study activation at Washington University [if single-center] / beginning six months after enrollment of the first patient at a secondary site [if multicenter], no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites and separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

In addition to regular submission of DSM reports to the DSMB, major protocol amendments must be reviewed by the DSMB prior to implementation. A major amendment is one that significantly changes the study design (e.g. addition or removal of an arm, addition or removal of a drug, significant change to the patient population, etc.). Further DSMB responsibilities are described in the DSMB charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB.

Audit Scheduling Guidelines

The first audit of a study should occur approximately 6 months (±2 months) after the first subject is enrolled, or earlier depending on accrual goals and actual recruitment. If no subjects have been enrolled 12 months after a study opens to accrual, QASMC will defer the study to PRMC. Subsequent audits are to occur at a frequency specified by the QASMC during recommendation deliberation for each audit report. Typically, studies are re-audited annually, but may be audited biennially, semi-annually, or after 3 months (e.g., for cause, or accrual driven). QASMC may use its discretion to waive or postpone an audit for small non-therapeutic studies with very low risk (e.g., auditor workload). Studies will not be re-audited until ≥2 new patients have been enrolled since the prior audit.

Guidelines for Rescheduling QA Audits

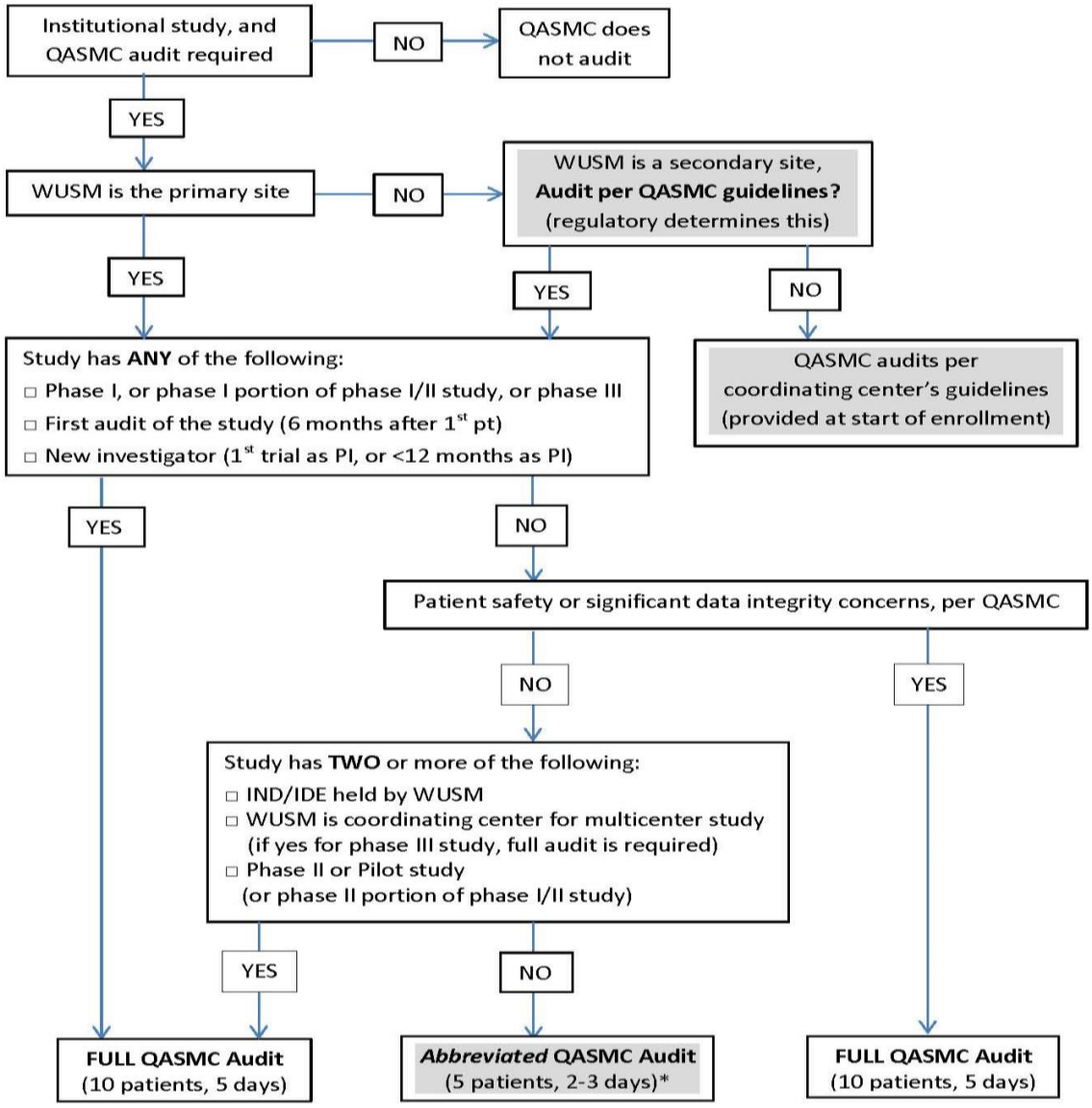
1. Audits will be rescheduled only in the case of an emergency or unavoidable situation, and not for the sake of convenience. Specifically, "staff turnover" will not be considered a sufficient rationale for rescheduling, as the expectation is that study personnel are routinely maintaining studies, and that seniors/managers/investigators are routinely overseeing this process. There may be times when seniors and/or managers may need to step in to prepare a study for audit.
2. Audits will not be rescheduled if the study is already ≥ 12 weeks overdue. If a study will not be ready for audit by the scheduled date, the study will be suspended to give the team time to prepare for audit.
3. Audits will be rescheduled for a date within 4-8 weeks before or after their due dates, on the condition that
    a. a time slot is available, or can be easily made available;
    b. the same manager requesting the schedule change is willing to reschedule one of his/her other studies
4. Advanced notice of ≥ 12 weeks will be required in order to reschedule an audit. In extreme cases, notice of ≥ 8 weeks may be allowed. This minimum lead time will allow 2 weeks to finalize the date change, 2 weeks to finalize the patient list, and 4 weeks for the coordinator to prepare for audit.

Guidelines to Determine the End of Audits

QA audits are ***not*** required for studies that are permanently closed to enrollment EXCEPT when:

1. The study has been audited only once before, and/or
2. ≥ 5 subjects enrolled since the prior audit (or ≥ 10% of all subjects, if the overall goal is >50), and/or ≥ 15 subjects were on treatment at some time since the prior audit (or ≥ 30% of all treated subjects), and/or on an as-needed basis at the discretion of the QASMC committee

Appendix B: Risk Based Auditing Schema



Appendix C: Siteman Cancer Center DSM Plan Flow Chart