



Quality Assurance and Safety Monitoring Committee (QASMC)

Policies and Procedures

October 22, 2020

Table of Contents

1.0 THE QUALITY ASSURANCE AND SAFETY MONITORING COMMITTEE (QASMC) 3

2.0 GOALS AND RESPONSIBILITIES OF THE QASMC 3

 2.1 Specific Responsibilities of the QASMC..... 4

3.0 QASMC MEETINGS 4

4.0 QASMC POLICIES AND PROCEDURES: UNANTICIPATED PROBLEMS (UPS) – ADVERSE EVENTS (AES)..... 4

 4.1 UP (AEs) Reporting Requirements 4

 4.2 UP Report Submissions..... 5

 4.3 UP Review Procedures..... 5

5.0 QASMC POLICIES AND PROCEDURES: DATA AND SAFETY MONITORING (DSM) REPORTS..... 6

 5.1 DSM Reporting Requirements 6

 5.2 DSM Documentation..... 6

 5.3 DSMB Membership 8

 5.4 DSMB Responsibilities:..... 8

 5.5 DSMB Meetings..... 9

 5.6 DSMB Recommendations..... 10

 5.7 Release of Outcome Data..... 10

 5.8 Confidentiality Procedures..... 11

 5.9 Conflict of Interest 11

6.0 QASMC POLICIES AND PROCEDURES: QUALITY ASSURANCE (QA) AUDITS 11

 6.1 Types of Quality Assurance 11

 6.2 Protocol Selection and Notification of Audit..... 12

 6.3 Case Selection 12

 6.4 Audit Frequency..... 13

 6.5 Risk-Based Auditing 13

 6.6 Low Accrual..... 13

 6.7 QA and Committee Procedures..... 13

7.0 PREPARATION FOR QA AUDIT 16

 7.1 Research Team Responsibilities..... 16

 7.2 Week of QA Review 16

APPENDIX A: DSM Plan Summary..... 18

APPENDIX B: Sample Wording of DSM Plans for Investigator-Initiated Trials 20

 Phase I Studies 20

 For multi-institutional Phase I studies consider an additional paragraph 20

 Phase II Studies 20

 For multi-institutional Phase II studies consider an additional paragraph..... 21

 Phase III Studies , Multicenter Studies, High-Risk Studies, or Other Studies with a DSMB .. 21

APPENDIX C: Audit Scheduling Guidelines..... 23

 Guidelines for Rescheduling QA Audits 23

 Guidelines to Determine the End of Audits:..... 23

APPENDIX D: Risk-Based Auditing Schema..... 24

1.0 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. See <https://siteman.wustl.edu/about/committees/> 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.

Conflicts of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page 11-12, 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, any QASMC committee member who is PI of a study 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.

2.0 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 institutional trials, reviewing all serious adverse events (SAEs) that occur on investigator-initiated research studies conducted under the auspices of the 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.

2.1 Specific Responsibilities of the QASMC

- Review data and safety monitoring (DSM) reports, which are typically submitted semi-annually
- Arrange for QA Advisors from its roster to provide expertise for QA audits
- Assess the trial audit findings of the QA Auditors and Advisors and making recommendations based on the findings
- Review in detail all SAEs occurring on investigator-initiated 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.

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

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.

4.0 QASMC POLICIES AND PROCEDURES: UNANTICIPATED PROBLEMS (UPS) – ADVERSE EVENTS (AES)

4.1 UP (AEs) Reporting Requirements

Unanticipated problem (UP) adverse event reports are submitted to the Washington University Human Research Protection Office (HRPO) [the institutional review board] per HRPO policies. QASMC receives UP reports on cancer-related protocols electronically from the protocol-specific research team(s) at the time review of the event by the IRB concludes. 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)

4.2 UP Report Submissions

Once the IRB has made a determination that an event meets the criteria to be considered a UP the event should be submitted to QASMC within 5 business days. Submissions should be sent to qasmc@wustl.edu.

The unanticipated problem reportable event form (REF) submitted to HRPO should be utilized for QASMC reporting.

Please note: All reportable UPs should be submitted to the HRPO per their policies, procedures, and/or recommendations, as a separate submission.

4.3 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), the Committee (or chair) will make one of the following decisions:

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 and copied to HRPO 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.

5.0 QASMC POLICIES AND PROCEDURES: DATA AND SAFETY MONITORING (DSM) REPORTS

5.1 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). Subsequent reports are required as defined 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, PRMC, and research team, as well as to the NCI Program Director responsible for funding the trial (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.

5.2 DSM Documentation

5.2.1 Single Institution Studies

Reports should be prepared by the research team or DSMB and signed and dated by the PI and statistician (where applicable) or Chair of the Board, 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, initial and most recent dates of approval, document dates, study status)
- History of study (including summaries of substantive amendments, accrual suspensions and reasons, protocol exceptions, errors, and breaches of confidentiality)
- Study-wide target accrual and actual accrual, as well as accrual by year by site (if applicable)
- Protocol activation date(s)
- Protocol objectives and a list of participants who have met each objective
- Measures of efficacy
- Early stopping rules and a list of participants who have met the rules
- Power analysis and/or interim analysis (if applicable)
- Summary of toxicities separated by site (if applicable) and cohort (if applicable)
- Abstract submissions
- Summary of recent literature
- Current consent form unless revisions made per SAE, then submit revised consent
- SAE cumulative summary

5.2.2 Multi-site Institutional Studies where WU is the Coordinating Center

Reports should include all relevant information as detailed above, incorporating data from all study sites including the cover sheet with the decision of the DSMB meeting signed by the DSMB members.

5.2.3 Multi-site Institutional 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. This report should also be reviewed by the PI at WU and submitted with a dated signature included with the outside DSMB report.

5.2.4 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/cover sheet from the DSMB (prepared and signed by DSMB chair)
- Current consent

- SAE summary

5.2.5 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 IRB submission will be forwarded to PRMC for further processing. In all cases, a copy of the final report and approval letter will be forwarded to the research team.

5.3 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. 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 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.

5.4 DSMB Responsibilities:

The DSMB must meet on a regular schedule (as defined by the protocol) over the course of study to review data relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, operating procedures, form completion, intervention effects, inclusion of women and minorities, and subject safety. Specifically, the DSMB is expected to:

- Assess the trial's overall utility based on its design and objectives;
- Identify problems related to patient safety;
- 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.); and
- Consider the rationale for continuation of the study and make a recommendation for or against continuation of the trial

5.5 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.

5.6 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

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 the recommendations from the current meeting. If concerns are identified, the report 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.

5.7 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.

5.8 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.

5.9 Conflict of Interest

A financial conflict of interest refers to situations in which it is reasonably determined a personal 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.

6.0 QASMC POLICIES AND PROCEDURES: QUALITY ASSURANCE (QA) AUDITS

6.1 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/clinical-research-resources/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.

6.2 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 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 only 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 less 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 at least one month ahead of the audit. Once accrual numbers are confirmed, 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.

6.3 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 .

6.3.1 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.

6.4 Audit Frequency

The first audit of a study should occur approximately 6 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, 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 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.

6.5 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 D). 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.

6.6 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.

6.7 QA and Committee Procedures

In preparation for the audit a QA Advisor is assigned and the protocol is reviewed with the QA Auditor. The QA Auditor will conduct a 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 Auditor will discuss the findings with the QA Advisor, as needed, and 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 Auditor revises the draft report and sends the final report to the research team. If a written response from the PI is required, it is due within 30 days of the date of the letter.

If an audit results in minimal and minor findings, the report will be sent via email to the QA Advisor for review and signature. Should the QA Advisor determine additional action is required, the report will be presented at the following month's QASMC meeting.

6.7.1 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 Auditor 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.

6.7.2 Evaluation of QA Findings

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

1. **Approved.** 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 response is required, a letter should be composed and will address each comment/recommendation outlined in the audit report. The letter will be signed by the PI and sent via email to the auditor. When a protocol revision is requested, the research team should prepare the appropriate IRB required documents and include these with the response to QASMC.

Given the importance of timely review, accrual will be suspended on those studies where the response to the audit is overdue by 120 days from the due date. A response is due 30 days from the date of the contingency letter. Reminder emails are routinely sent for overdue response. If a response is not received within 90 days of its due date, a 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.

6.7.3 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 to the PRMC to close the study.

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 the audit is approved, an approval letter will be sent to the PI and team via email. Primary team members, managers, and HRPO will be copied on the email.

7.0 PREPARATION FOR QA AUDIT

7.1 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.

7.2 Week of QA Review

The research team will make arrangements for providing regulatory files and patient charts to the auditor and for granting access to case report forms and applicable databases. The PI is not required to be available during the audit week but a research coordinator should be available to address questions.

APPENDIX A: 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. Instructions for completing these templates for these reports are provided on the Siteman Cancer Center webpage <https://cbmiapps.wustl.edu/confluence/display/OSS/3.+DSM+Reports>.

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 is;
 - a. 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 DSMC. 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 research team and assessed by the 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
 - d. Summary of any recent literature reporting developments that may affect safety or ethics of study.

APPENDIX B: 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, error, or breach 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
- 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 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 a 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.

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 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
- 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
- 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 separated by cohorts
- 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 a 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.

For multi-institutional Phase II studies consider an additional paragraph.

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. Semi-annual DSM reports will include a summary of the data from all sites, including adverse events and responses. DSM reports will be distributed to the responsible investigator at each participating institution.

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.

APPENDIX C: 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-interventional studies with very low risk (e.g., auditor workload). Studies will not be reaudited until ≥ 2 new patients have been enrolled since the prior audit.

Note: Audit dates must be confirmed by regulatory and clinical team managers ≥ 3 months (preferably ≥ 6 months) in advance of the due date.

Guidelines for Rescheduling QA Audits:

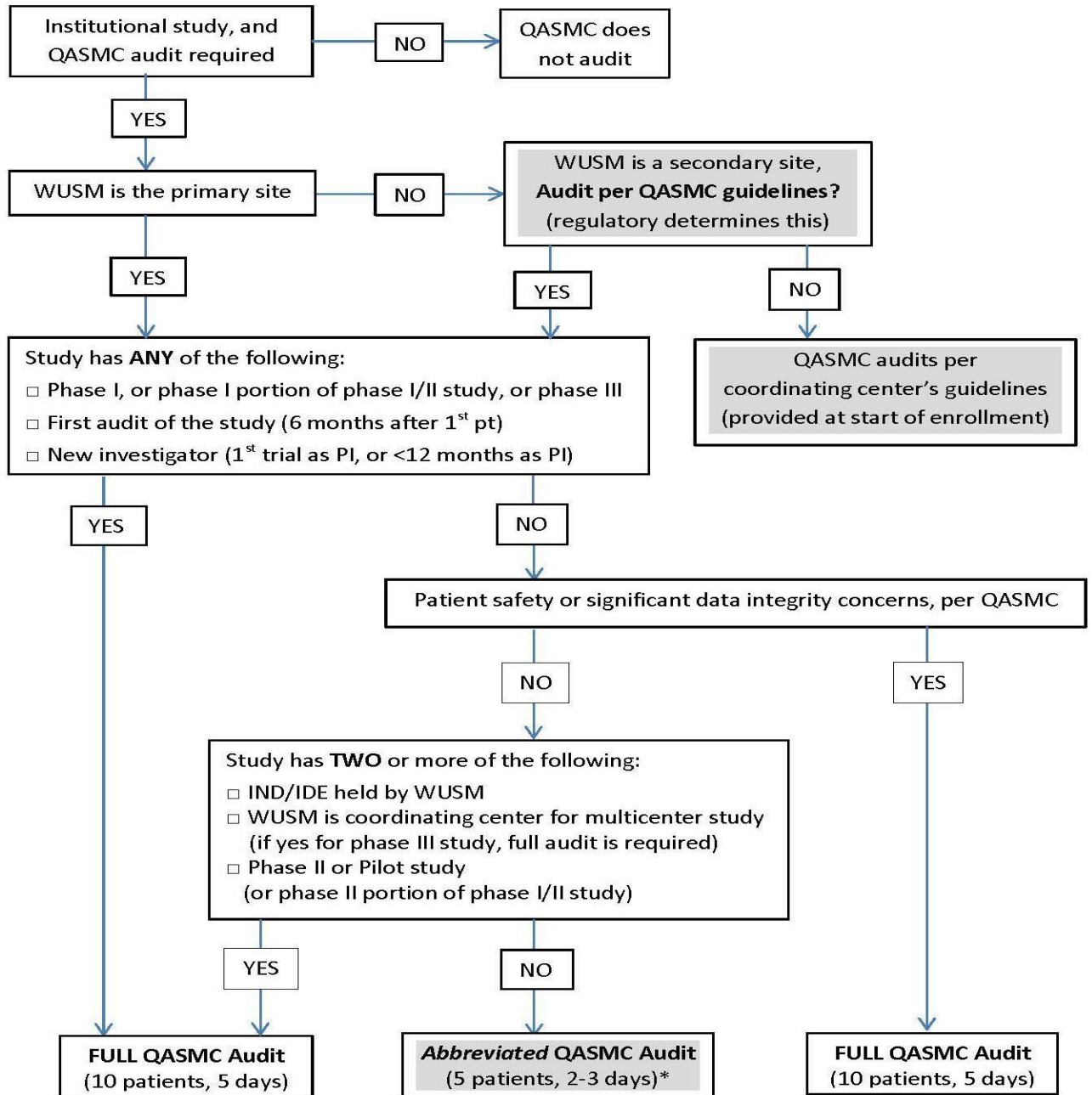
1. Audits will be rescheduled only in the case of an emergency or unavoidable situation, and not for the sake of convenience. Specifically, “staff turnover” will not be considered a sufficient rationale for rescheduling, as the expectation is that study personnel are routinely maintaining studies, and 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:

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

APPENDIX D: Risk-Based Auditing Schema



*If abbreviated QASMC audit is required, this must meet the auditing requirements of the coordinating center when WUSM is a secondary site. Re-audit may occur in 6, 12, 18 or 24 months, as the QASMC recommends.