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University of Iowa Health Care
Holden Comprehensive Cancer Center

Institutional Data and Safety Monitoring Plan

Policy and Procedures

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Introduction

In accordance with the National Institutes of Health (NIH) policy on procedures for data and safety monitoring of clinical trials, the Holden Comprehensive Cancer Center (HCCC) has developed systems to ensure:

- the safety and rights of research participants,
- the validity and integrity of research data, and
- compliance with the approved protocol and regulatory requirements.

HCCC principal investigators are required to include a general description of a data and safety monitoring plan as part of each new interventional (treatment and non-treatment) research protocol that they develop and submit for review.

Interventional clinical trials authored by outside agencies (e.g. industry, cooperative group and other consortia) but conducted at University of Iowa Health Care (UIHC) by HCCC physicians as participating investigators, must also include appropriate provisions for monitoring participant safety commensurate with the type and phase of trial and the potential for risk.

The DSMP is the institutional document that integrates requirements for

- data and safety monitoring,
- adverse event and serious adverse event (SAE) reporting, and
- protocol deviation reporting

This document provides an overview of the review and approval processes for cancer clinical research at the University of Iowa and Iowa Health Care, and describes the integrated requirements for monitoring, adverse event reporting, protocol deviation reporting, and safety oversight.

<u>Clinical Protocol and Data Management</u>

Clinical Protocol and Data Management (CPDM) efforts are managed through Clinical Research Services (CRS) of the HCCC through two related components –

1. The Clinical Trials Support Office (CTSO):
   Provides centralized services for protocol development, submission, routing, IRB renewal, amendments, adverse event/SAE monitoring, accrual tracking, screening/consenting support, data management, quality assurance, and investigator training,
2. Data and Safety Monitoring (DSM):
   Coordinated through the Data and Safety Monitoring Committee (DSMC), which reviews cumulative safety data, protocol deviations, monitoring reports, and overall compliance with regulatory and protocol requirements.

These components are critical shared resources that support clinical cancer research including treatment, non-treatment interventional and non-interventional studies conducted by members of the HCCC.
Together, these shared resources support investigator-initiated trials (IITs), NCI's National Clinical Trials Network (NCTN) trials, consortium trials, and industry sponsored trials conducted by HCCC members. .

As part of HCCC's growing institutional footprint, Mission Cancer + Blood serving central and western Iowa, is fully integrated into HCCC DSMC oversight. All investigator-initiated research activities conducted there are governed under the HCCC DSMP. Accordingly, Mission's protocols undergo the standard review process through PRMC and DSMC, adhere to OnCore-based data and safety monitoring,

and comply with multi-center monitoring/audit requirements outlined in Appendix 2, and follow institutional SAE and deviation reporting requirements

Protocol Review and Monitoring System

The goal of the Protocol Review and Monitoring System (PRMS) at the HCCC is to ensure the highest scientific quality of clinical oncology research is conducted at the HCCC. A two-step review process is used.

1. Trial concepts are first reviewed by the disease-specific Multidisciplinary Oncology Groups (MOGs) and the Trial Resource Evaluation Committee (TREC) to assure there is adequate resources and support for a concept before extensive effort is placed on development of a full protocol.
2. Once the protocol is developed, it is reviewed by the Protocol Review and Monitoring Committee (PRMC) that approves, defers the protocol for further development, or disapproves the protocol and assigns a priority score.

The PRMC also monitors accrual and receives summary reports of monitoring findings of ongoing clinical trials. The PRMC has the authority to close protocols that do not demonstrate scientific progress or that are no longer addressing a scientifically valid question.

Institutional Oversight of HCCC Clinical Trials – Required Reviews Prior to Protocol Activation

Multidisciplinary Oncology Groups (MOGs)

To ensure efficient use of HCCC resources for clinical trials, concepts/protocols must be initially approved and prioritized by the appropriate disease specific Multidisciplinary Oncology Group (MOG). MOG review is required to assure there is adequate support for a concept before extensive effort is placed on development of a full protocol. Final approval by the TREC and PRMC are contingent upon approval by the applicable MOG.

Trial Resource Evaluation Committee (TREC)

Prior to PRMC submission, protocols utilizing HCCC Clinical Research Services (CRS) must be reviewed and approved by the Trial Resource Evaluation Committee (TREC). The TREC is comprised of physicians with expertise in various cancer disease sites, pharmacy representatives, clinic and infusion suite leadership, and management from clinic research services. The committee assesses trial feasibility by reviewing all resources needed to conduct a proposed trial. It reviews logistical issues associated with required study activities and enrollment. In addition, TREC proactively scrutinizes eligibility criteria for each proposed trial and identifies both clinical and research logistical accrual challenges with the goal of remediating them pre-emptively to optimize accrual workflow.

University of Iowa Institutional Review Board (IRB)

The Human Subjects Office – Institutional Review Board (IRB) is the institutional body that reviews all studies that involve human subjects. The IRB is charged with the protection of human subjects participating in research, regardless of whether the research is subject to federal regulation and regardless of sponsorship. It is responsible for reviewing proposed research involving human subjects to ensure protection of those subjects and compliance with federal human subject regulations.

IRB membership consists of University of Iowa faculty and staff as well as lay and professional representatives from the community. The IRB reviews research that:

- is sponsored by the institution, or
- is conducted by or under the direction of any employee or agent of the institution (including students) in connection with his or her institutional responsibilities, or
- is conducted by or under the direction of any employee or agent of the institution using any property or facility of this institution, or
- is conducted by any employee or agent of the institution (including students) who meets the criteria for "engaged in research" as defined in OHRP guidance of October16, 2008 (http://www.hhs.gov/ohrp/policy/engage08.html), or
- involves the use of this institution's non-public information to identify or contact human subjects.

Prior to full IRB review, additional institutional bodies must also review protocols (e.g. the Joint Office for Compliance, the Medical Radiation Protection, Pharmacy and Therapeutics (P&T), and Investigational Drug committees). Final approval of the study and release of the stamped informed consent document occurs only when the PI has satisfactorily addressed each committee's critique, and the Protocol Review and Monitoring Committee (PRMC) and other appropriate reviewing bodies have each given their respective approval.

The IRB does not review the scientific merit of cancer related protocols but does review the safety and ethical issues associated with each protocol. This includes evaluating the informed consent document, the proposed process for recruiting subjects, and details of the data and safety monitoring procedures for protocols with potential risk to participants.

New cancer protocols are submitted to and reviewed by the IRB using an electronic application system (HawkIRB). Protocol submission to the IRB and PRMC may occur concurrently, and IRB approval may be granted prior to PRMC approval. However, the project will not be released in HawkIRB until the project receives all applicable HRPP approvals. Upon submission of the application, an automatic email notification is sent to the administrative office (Protocol Development and Monitoring) for the DSMC and the PRMC located within the Clinical Research Services of HCCC. Protocol Development and Monitoring (PDM) staff also receive an automatic notification from HawkIRB when IRB approval, continuing reviews, modifications, reportable events, and study closures occur. All reviews and events in the life cycle of a study are recorded in the institution's clinical trials management system (CTMS), OnCore.

HSO/IRB Mandatory Certification of All Clinical Investigators

University of Iowa policy requires all investigators and their staff conducting research with human subjects to complete an education program and become "certified" in human subject protections through the Collaborative Institutional Training Initiative program (CITI). Some investigators with funding sources such as the NIH and NSF may also be required to complete additional training provided by the University of Iowa Responsible Conduct of Research (RCR) Plan. Final IRB approval for any clinical trial is contingent on all investigators listed on the protocol being certified. A comprehensive list of certified University of Iowa employees is maintained by the administrative office of the IRB, the Human Subjects Office (HSO), and is available on the HSO website.

Conflict of Interest in Research Policy

Federal regulations place responsibility for determining the existence of a financial conflict of interest (COI) in research on the institution rather than the investigator. All University of Iowa researchers must disclose financial interests in outside entities in the eCOI Disclosure System. The University of Iowa Conflict of Interest in Research Office reviews the disclosures in the context of all routing forms and IRB applications.

The COI in research policy applies to all individuals involved in research at the University, regardless of job title, who contribute in a substantive way to the development, execution, and reporting of research, and who are granted a significant degree of freedom in exercising independent judgment.

Protocol Review and Monitoring Committee (PRMC) Review

New research protocols involving cancer patients are reviewed by the Cancer Center's Protocol Review and Monitoring Committee (PRMC). This committee is charged with the review of the scientific merit (hypothesis, objectives, design, sample size, biostatistics), prioritization with existing studies, and the adequacy of provisions for monitoring the safety of subjects via the data and safety monitoring plan.

Structural Organization

The PRMC is comprised of a:

- Chair (board eligible or certified medical, surgical, gynecological, radiation or pediatric oncologist)
- Co-chair(s) (board eligible or certified medical, surgical, gynecological, radiation or pediatric oncologist)
- Representatives from clinical departments involved in cancer care as well as representatives from the basic sciences (scientific review)
- Biostatistician(s) (review of design/data analysis plans)
- Clinical Pharmacy Specialist(s) (P&T review)
- Patient Advocate(s)
- PRMC administrative staff (non-voting)
- DSMC compliance staff (non-voting)

Within the organization the committee chair reports to, and is advised by, the Associate Director for Clinical Research. The Committee's operations are entirely separate and distinct from the IRB. The PRMC has the authority to terminate clinical trials based on poor accrual, recommendations from the DSMC, or a change in the relevance of the research.

Protocol Submission and Review

All clinical studies that involve cancer patients at the University of Iowa Health Care and,

- are HCCC investigator-initiated, or
- are non-HCCC investigator-initiated, or
- are NCTN, consortia, or industry-sponsored

must be submitted to the PRMC for review. All investigator-initiated trials must include a Data and Safety Monitoring Plan (DSMP) that will be reviewed by the DSMC Chair/designee prior to final PRMC approval. All investigator-initiated protocols must also be reviewed and signed off by a statistician prior to PRMC submission. Investigators are strongly encouraged to consult with the HCCC Biostatistics Core during protocol development. The HCCC Investigator-Initiated Trial Protocol Working Group is a multidisciplinary forum designed to support clinical investigators in the development of cancer-related IITs. The group aims to foster innovation, enhance scientific rigor, and streamline the development process for investigator-initiated oncology trials. The Working Group is composed of faculty, DSMC administrative staff, statistician, regulatory, finance, and pathology experts. The Working Group meets biweekly and is available to review and provide feedback to investigators on early development or trial concepts for IITs.

The PRMC meets twice monthly to review new investigator-initiated and industry protocols. NCTN protocols are administratively reviewed by the committee Chair or Co-Chair throughout the month. Committee review results in a protocol being fully approved, conditionally approved (response required from the PI), tabled, deferred for further development, or disapproved.

Ongoing Review by the PRMC

IRB continuing reviews and modifications to active clinical trial protocols are monitored by HCCC PDM staff for the PRMC and the DSMC. All IRB approvals are automatically sent to OnCore and each event is reviewed by PDM staff. Changes to eligibility, study design, and objectives are noted and updates are made to trial documents, safety plans, public trial listings and database records. Significant changes to a study may result in an administrative review by the PRMC and/or DSMC chairs, or a full PRMC review.

The accrual rate for each active study is monitored by the PRMC to ensure adequate progress. Investigators on trials demonstrating consistently low accrual rates are queried by the committee Chair and are required to provide written justification for continuing the study.

The PRMC maintains standard operating procedures for the review and ongoing monitoring of clinical trials. The PRMC requires the PI to specify in the body of the protocol:

- expected toxicities for all study drugs,
- the appropriate stopping rules,
- criteria for suspension of accrual secondary to adverse events and safety parameters,
- guidelines for reporting routine and expedited adverse events, and
- level of risk, with description of DSMC approved data and safety monitoring procedures.

The PRMC has the authority to close any cancer protocol that is not performing to expected standards.

The primary reasons an existing trial may be closed are:

- The study question has become obsolete by virtue of new scientific information.
- Accrual of subjects to the study is either complete or will not meet accrual goals in a reasonable time (as set forth in the SOP on accrual).
- Significant concerns regarding trial data and subject safety are raised by DSMC review and further assessment by the PRMC.

When a trial meets the criteria for stopping or suspension for any reason subject to further review:

- The PRMC Chair will communicate this to the IRB Chair and the Principal Investigator (and in the case of multi-site studies, participating PIs). This communication will indicate the mandatory cessation of further enrollment on the trial. A letter to the PI will be sent immediately detailing the reasons for the change in study status. This letter is to be signed by both the PRMC Chair and the Director of the HCCC.
- For NCI or industry-sponsored studies, the IRB Chair or designee is responsible for communication with the appropriate personnel in the office of the University of Iowa Vice President for Research, Division of Sponsored Programs, who will, at the earliest possible time, communicate this to the Project Officer at the NCI or other external funding agency. If the trial is re-opened, this information will be recorded and communicated in like manner.

Data and Safety Monitoring Committee (DSMC) Review

The Data and Safety Monitoring Committee (DSMC) has a separate and distinct function from the PRMC and IRB. Its primary tasks are to:

- review the eligibility of patients entering HCCC interventional, investigator-initiated trials for trial-specified eligibility,
- assess subject safety by reviewing adverse and serious adverse event (AE/SAE) reports and ensure timely and appropriate reporting to oversight agencies (e.g. NCI, FDA, IRB),
- monitor clinical trials (via routine reviews by the study monitor) for data veracity and integrity, subject safety (AE/SAE records), and protocol compliance,
- review monitoring reports, incidents of unexpected toxicity, accrual to institutional trials, deviations and make recommendations to the PRMC when suspending or terminating a study as deemed appropriate
- provide consultation and education to investigators regarding issues of subject safety and the development of acceptable data and safety monitoring plans

The DSMC will use DSMC monitoring reports and protocol stopping rules to determine whether a study warrants closure. All external audits must be submitted to the DSMC, whether from Industry Sponsor audits or from NCI audits for review at DSMC meetings.

Structural Organization

The DSMC is composed of a:

- Chair: Board eligible or certified in an oncological specialty
- Co-chair: Board eligible or certified in an oncological specialty
- Biostatistician-Review of study design and data analysis plans.
- Clinical research member(s) of the HCCC
- Clinical Pharmacist(s)
- Research nurses and study coordinators
- Ad hoc, protocol-specific Study Monitors (non-voting)
- DSMC compliance staff (non-voting)
- DSMC administrative staff (non-voting)

All voting committee members are appointed to a 2-year renewable term by the executive leadership of the HCCC (Director and Associate Directors).

A quorum for the DSMC consists of 60% of the total committee membership. A quorum must be present in order to conduct DSMC business at any regularly scheduled meeting. The DSMC convenes approximately every 6 weeks to review safety data for ongoing IITs, perform review for dose escalation and other cohort review requests, monitoring reports, SAEs and deviations. The committee documents its decisions and recommendations via a letter that is sent to the PI and applicable research team members following the meeting.

Conflict of Interest: Committee members who are also investigators on a trial under review must recuse themselves from voting on matters related to that trial, including decisions of protocol violations or study suspension. . As an investigator, however, they may be viewed as a resource for information about their trial and may attend meetings when only general discussions (accrual, monitoring reports, etc.) are on the agenda.

Inclusion of a DSMC-Approved Data and Safety Monitoring Plan

All investigator-initiated protocols must include an appropriately detailed Data and Safety Monitoring Plan (DSMP) outlining:

- Monitoring procedures
- SAE reporting, and
- Protocol deviation reporting.

The DSMC Chair reviews all interventional IITs' DSMPs prior to PRMC approval. The DSMC determines what constitutes an adequate plan based on the phase, complexity, and risk level of the study.

All interventional clinical trials, including physiologic, toxicity- and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III), require monitoring for protocol compliance, data veracity and subject safety. The method and degree of monitoring needed is related to the degree of risk and should also be commensurate with size and complexity of the trial.

Risk-Based Monitoring Approach

The DSMC utilizes a risk-based monitoring approach in its routine review of investigator-initiated trials. Risk-based monitoring is the process of ensuring the quality of clinical trials by identifying, assessing, monitoring and mitigating the risks that could affect the quality or safety of a study. FDA guidance outlines three steps in a risk-based approach to monitoring:

1. Identify critical data and processes. To accurately monitor the quality of a study and the safety of its participants, the DSMC must know which elements are most important for each particular study – from informed consent to eligibility screening and tracking of adverse events.
2. Perform a risk assessment. A risk assessment involves determining specific sources of risk and the effect of study errors on those risks.
3. Develop a monitoring plan. A monitoring plan should describe the monitoring methods, responsibilities, and requirements of the trial. The plan should include information on the risks, monitoring procedures, and responsibilities of all personnel involved in monitoring the trial.

NCTN trials are monitored under group-wide DSMPs and are not required to have a separate institutional DSMP. In the case of industry-sponsored studies that do not have an internal or external

monitoring board or functional equivalent, the DSMC will require a letter of assurance that safety monitoring procedures conform to all applicable local, federal and international regulations governing the protection of human subjects.

Mission Cancer + Blood, Iowa Health Care is now recognized within the HCCC's institutional oversight structure. All interventional investigator-initiated studies conducted through Mission fall under HCCC DSMP protocols and are reviewed by the DSMC according to risk-based criteria.

Required Elements of a Data and Safety Monitoring Plan

1. The Principal Investigator for institutional studies at the HCCC must include a trial-specific DSMP with each new protocol. The DSMP may be included in the body of the protocol or attached as an appendix. Changes to the DSMP as a result of subsequent protocol modifications should be noted either in the protocol as a change memo or as a revised DSMP document. The key items the plan must include are:
    - Assigned level of risk to subjects (as defined below),
    - Subject eligibility criteria (inclusion / exclusion, typically in a checklist format)
    - For interventional treatment and non-treatment trials:
        - A list of expected toxicities
        - Stopping rules for suspension of accrual secondary to AE/SAEs
        - The DSMP must identify key elements of the trial that are critical to data integrity, outcome measures, and subject safety
        - SAE reporting timelines and responsibilities
        - Protocol deviation reporting
    - For non-interventional trials:
        - A list of potential subject risks (e.g. fatigue, emotional distress, breach of confidentiality)
        - Rules for subject withdrawal
    - For multi-centered interventional treatment trials, where HCCC is the lead organization, a detailed description of the procedures in place at each center that enable communication between participating centers such that the PI is aware of the status of participating subjects, including the immediate (<24hours – weekday) awareness of grade 4 – 5 SAE / death (see Appendix 2 for additional multi-center guidelines).
    - For multi-centered interventional treatment trials, in which HCCC is a participating site, contact information for the lead institution to arrange for receipt of data and safety monitoring reports and DSMC recommendations.
2. This plan must be approved by the DSMC, which will make the final determination of the type of data and safety monitoring process that will be required for the protocol according to the guidelines below. The approved plan will be part of the clinical trial material reviewed by the PRMC. If a DSMC-approved DSMP has been omitted from the submitted documents, it will be required before final PRMC approval can be granted.
3. The Principal Investigator is to ensure that all required data for monitoring is provided to the DSMC by way of the study monitor.
4. The Principal Investigator will provide an annual progress report to the DSMC:

- The current status of the study, monitoring/auditing history, accrual history, an overview of AE/SAEs, protocol deviations, survival, and response information (as applicable) for aggregate review by the committee.
- For 2 studies, applicable information will be exported from OnCore or Advarra EDC by HCCC DSMC staff for annual administrative review by the DSMC Chair or designee. Review documentation indicating approval for the study to continue enrollment along with any questions, suggestions, or DSMC requirements for modification to the protocol will be sent to the PI. This documentation should be submitted to the IRB at the time of the next Continuing Review.
- For Risk Level 3 and 4 studies, this information will be exported from OnCore or Advarra EDC by HCCC DSMC staff for annual review at DSMC meetings. Review documentation indicating approval for the study to continue enrollment along with any questions, suggestions, or DSMC requirements for modification to the protocol will be sent to the PI. This documentation should be submitted to the IRB at the time of the next Continuing Review.

Data and Safety Monitoring at the HCCC

Determination of the Level of Data and Safety Monitoring

Risk Level 1 (Minimal Risk)

Non-physical, interventional and non-interventional studies with a low risk of morbidity or death,* (<1% of death or any adverse event), e.g. observational, epidemiologic, laboratory use of left over samples from clinically indicated procedures,

and

Physical, interventional studies with a low risk of morbidity or death, * (<1% of death or any adverse event), e.g. behavioral surveys and questionnaires, music therapy, coping strategy assessment, nutrition assessment, healing touch studies, imaging (not using sedation), EKGs and gait assessments.

Study Safety Review

The PI or designated study personnel will review all study data for completeness, enrollment, protocol deviations, drop-outs andadverse events. .

Additional Reporting Requirements

- Subject accrual data will be obtained from OnCore on an ongoing basis by PDM staff during accrual review for the PRMC.
- Adverse events will be documented and reported to the DSMC as defined in the DSMP for the study.
- All Risk Level 1 studies are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting

Risk Level 2 (Low to Moderate Risk)

Interventional trials with a risk of death* (<1% or any adverse event 1% – 5%), e.g. behavioral interventions, nutritional therapies, low risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin or muscle biopsy, nasal wash, lumbar puncture, bone marrow biopsy, imaging requiring sedation), as well as therapeutic trials involving agents with known safety profiles already licensed for the indication and age group. Most disease-prevention trials will be considered at least a Risk Level 2.

Study Safety Review

The PI or designated study personnel will review all data, including completeness of study data, enrollment, protocol deviations, drop-outs, adverse events on a regular basis and provide an annual report to the DSMC and PRMC.

Additional Reporting Requirements

- Subject accrual data will be obtained from OnCore on an ongoing basis by PDM staff during accrual review for the PRMC.
- A member of the research team will register new subjects in OnCore.
    - Depending on the complexity of eligibility criteria, the research team may also be required to upload a scanned copy of the completed eligibility checklist, with screening information and PI signature, in OnCore for review by the study monitor.
- Adverse events will be documented and reported to the DSMC as defined in the DSMP for the study.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and/or staff for review.
- All Risk Level 2 studies are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting

Risk Level 3 (Moderate Risk Interventional Trials)

Interventional treatment and non-treatment trials with a risk of death* (1% – 5% or grade 4 – 5 SAE 1% – 5%), e.g. moderate risk procedures Phase I or II clinical trials with available safety data in humans, studies treating subjects with placebo for a recognized disease, and trials with risk of radiation exposure.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least annually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs. DSMC monitoring reports should also be submitted to the IRB at the time of Continuing Review.

Additional Reporting Requirements

- Subject accrual data will be obtained from OnCore on an ongoing basis by PDM staff during accrual review for the PRMC.
- The research team will register new subjects in OnCore. A scanned copy of the completed eligibility checklist, with supporting source documentation and PI signature, consent and consent documentation will be attached in OnCore for ongoing review by the study monitor.

- Adverse events will be documented and reported to the DSMC within 24 hours of awareness as defined in the DSMP for the study.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to DSMC Chair/acting Chair and/or staff for review.
- Deviations from the written protocol must be reported in OnCore. Deviations affecting subject safety, primary endpoints, or drug accountability must be reported in OnCore within 7 working days and via a Reportable Event Form (REF) to the IRB within 10 working days of the PI becoming aware of the event.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum once per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. A minimum of 25% of subject records will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - check for the presence of a signed informed consent and documentation of consent process
  - Review adherence to treatment plan, including Investigational Product (IP) orders, drug doses, dose reductions and/or treatment holds, if indicated
  - determine compliance with protocol's study plan, including assessment of primary and key secondary endpoint data
  - determine if deviation from the protocol are recorded and reported in OnCore, the IRB of record and external regulatory agencies as applicable
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy, adequacy, completeness, and timeliness of data collection in the research record and EDC data entry with the primary source documents,
  - review quality of source documentation to ensure that records are attributable, legible, contemporaneous, original, accurate, and complete
  - review of dose limiting toxicites as applicable
  - determine whether patient follow up requirements are met
  - review investigational drug processing and documentation,
  - assess cumulative AE/SAE reports for trends and compare to study stopping rules,
  - review of regulatory documents

Risk Level 4 (High Risk/IND/Gene Therapy/First in Human Trials)

Interventional treatment trials involving investigational agents or devices with a risk of death*(>5% or grade 4 – 5 SAE >5%), e.g. all investigator initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs. DSMC monitoring reports should be submitted to the IRB at the time of Continuing Review.

Additional Reporting Requirements:

- Subject accrual data will be obtained from OnCore on an ongoing basis by the PDM staff during accrual review for the PRMC.
- The research team will register new subjects in OnCore. A scanned copy of the completed eligibility checklist, with supporting source documentation and PI signature, consent and consent documentation will be attached in OnCore for ongoing review by the study monitor.
- Adverse events will be documented and reported to the DSMC as defined in the DSMP for the study.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team within 24 hours of awareness OnCore will send an automatic notification to the DSMC Chair/acting Chair and/or staff for review.
- Deviations from the written protocol must be reported in OnCore. Deviations affecting subject safety, primary endpoints, or drug accountability must be reported in OnCore within 7 working days and via a Reportable Event Form (REF) to the IRB within 10 working days of the PI becoming aware of the event.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. A minimum of 25% of subject records will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - Review adherence to treatment plan, including Investigational Product (IP) orders, drug doses, dose reductions and/or treatment holds, if indicated
  - check for the presence of a signed informed consent and documentation of consent process,
  - determine compliance with protocol's study plan, including assessment of primary and key secondary endpoint data
  - determine if deviation from the protocol are recorded and reported in OnCore, the IRB of record and external regulatory agencies as applicable
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy, adequacy, completeness, and timeliness of data collection in the research record with the primary source documents,
  - review quality of source documentation to ensure that records are attributable, legible, contemporaneous, original, accurate, and complete
  - review of dose limiting toxicites as applicable

- determine whether patient follow up requirements are met
- review investigational drug processing and documentation,
- assess cumulative AE/SAE reports for trends and compare to study stopping rules,
- review of regulatory documents

** "risk of death" refers specifically to 100-day treatment-related mortality*

Compassionate Use or Expanded Access

Drugs being used on a compassionate or expanded access basis are available in the HCCC because an investigator has agreed to be the investigative sponsor.

The DSMC will monitor:

- eligibility
- serious adverse events
- ultimate outcome
- patients enrolled on these studies. The sponsoring investigator will be the responsible HCCC agent for a drug's use.

Adverse Event Reporting

Adverse Events

It is a requirement that each protocol have specified guidelines regarding the identification of, and procedures to be followed for, the investigation and reporting of adverse events [AE]. An AE is defined in the *CTEP, NCI Guidelines* [2024] as "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probably or definite)." These procedures must delineate when such reporting is to occur, to whom and who specifically is charged with ensuring appropriate reporting takes place.

Each investigator is required to report adverse events in a timely manner to the DSMC via the assigned monitor as well as the appropriate regulatory authority. ("Reports to DSMC" means that the report is available for review by the DSMC monitor in OnCore or Advarra EDC and communicated to the DSMC.)

The adverse event may also require reporting to the IRB. For IRB reporting requirements please refer to the University of Iowa Human Subjects Office (HSO) website.

The timing of these reports is defined below. Cumulative SAEs will be monitored by the DSMC for trends and compared to stopping rules for the specific study.

Protocol Deviations

Deviations are any departures from the protocol, study plan, or regulatory requirements.

Major deviations (those impacting subject safety or rights, data integrity, or eligibility) must be reported in OnCore within 7 working days and via a Reportable Event Form (REF) to the IRB within 10 working days of the PI becoming aware of the event. Major deviation reports with corrective and preventive action (CAPA) plan, if required, and other supportive documentation will be reviewed by the DSMC chair and statistician, if applicable.

Minor deviations (those that do not affect the safety of a subject or study outcomes) must be logged in OnCore within 7 working days of the PI becoming aware of the event and will be reported to the IRB at the time of Continuing Review.

A DSMC monitor will review IIT protocol deviations reported via OnCore to determine if the protocol deviation is documented and reported accurately. The information reported in OnCore will be source verified.

The DSMC reviews deviation trends to assess study conduct, implement corrective actions, and determine if retraining or suspension is required.

CTEP, NCI Guidelines: Adverse Event Reporting Requirements

The CTEP, NCI guidelines provide the underlying structure for adverse event reporting by investigators on HCCC institutional protocols. However, the guidelines are flexible and allow for exceptions to general reporting requirement, but these must be *clearly stated as protocol-specific requirements* in the protocol. Clinical investigators, and ultimately the Principal Investigator, have the primary responsibility for AE identification, documentation, grading, and assignment of attribution. Protocol specific AE/SAE reporting requirements should consider the following factors:

1. Phase of the trial
2. Criteria for unexpected vs. expected toxicities
3. Commercial agent used as standard of care or a commercial agent used under an IND
4. Investigational agent under a CTEP, NCI or other external agency's IND
5. Routine reporting vs. expedited reporting

Commercial Agent

A commercial agent may also be used as an investigational agent (under an IND). Refer to the protocol document to determine if an agent is being used as an investigational or commercial agent for the protocol. In general, only Grade 4 and 5 events that are unexpected with at least "possible" attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions.

Documenting Routine Adverse Events (AEs)

For non-serious Adverse Events, documentation must begin from the first day of study treatment and typically continues through the 30 day follow-up period after treatment is discontinued. Some protocols may require different timelines for AE reporting.

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Terminology Criteria for Adverse Events

(CTCAE)http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The Principal Investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Reporting Serious Adverse Events (SAEs)

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event typically begins after signing of the informed consent and continues through the 30 day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event. Updates on the event should be recorded weekly in OnCore until resolution. The final SAE report must be completed in OnCore no later than 7 (seven) days from the date the SAE is resolved.

A DSMC monitor will review IIT SAEs reported in OnCore to determine if the SAE is documented and reported accurately and in a timely matter. The information in OnCore will be source verified.

An adverse event is considered serious if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Additional Reporting Requirements

FDA Reporting Requirements

HCCC study personnel are responsible for informing the Principal Investigator of the SAE, and, if it is also unexpected, for forwarding all MedWatch 3500A forms to the FDA in accordance with 21 CFR 312.32 (for drugs under an IND) and 21 CFR 314.80 (for marketed drugs).

For multi-site trials, the PI is responsible for informing each Affiliate Principal Investigator of all serious and unexpected SAEs or AEs.

IRB Reporting Requirements

The Principal Investigator (PI) is responsible for promptly reporting all serious adverse events (SAEs) that are serious, unexpected and possibly, probably or definitely related to the study participation. Such events must be reported to the Institutional Review Board (IRB) as soon as possible, but no later that ten (10) calendar days from the time the PI becomes aware of the event.

The PI must also report any other events that meet the IRB's criteria for reportable events (e.g., unanticipated problems involving risks to subject or others, protocol deviations, or noncompliance) in accordance with the IRB reporting policies and procedures.

All SAEs and reportable events must also be summarized and submitted to the IRB at the time of continuing review.

Sponsor Reporting Requirements

The PI is responsible for meeting reporting requirements to applicable external sponsors.

Data Monitoring and Management

Subject Registration

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Each subject registration includes the following:

- The subject's IRB approved (version date) consent form and the date of their consent.
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

All subject registration information is expected to be entered into OnCore within **2 (two) business days** after the subject's study visit.

Subject Data

For HCCC investigator initiated trials, research staff are responsible for entering subject study data (data collection) into OnCore or Advarra EDC electronic case report forms (eCRFs). These eCRFs must be approved by the PI and statistician prior to study activation to ensure sufficient and necessary data acquisition. All information entered into eCRFs will be traceable to the source documents which are generally maintained in the subject's file and uploaded to OnCore.

eCRF data entry needs to be timely and should be entered into OnCore or Advarra EDC as soon as possible but no later than **14 (fourteen) business days** after the subject's visit, including adverse events, tumor measurements, administration of study medication, concomitant medications, labs, and vitals.

Physical exam assessments must be entered no later than **14 (fourteen) business days** following completion of the physician's clinic note in the medical record.

Timely data entry facilitates remote monitoring of data, allows the data to progress appropriately through the data cleaning process, and helps prevent a backlog of data queries.

Forms Monitoring

OnCore and Advarra EDC eCRF data are monitored on a routine basis (dependent on accrual) to ensure all data are entered completely, accurately, and within time requirements outlined above. The assigned DSMC monitor will coordinate and complete the data monitoring review. When the time comes to monitor a study (based on patient accrual and assigned risk level of trial) the monitor arranges for a selection of cases to be reviewed from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries via OnCore or Advarra EDC (linked to the eCRF) to resolve missing, incomplete, and/or incorrect information. A member of the research team is expected to respond to these monitoring queries within **14 (fourteen) business days.**

The monitoring process can often identify misunderstandings or deficiencies in the written, research protocol requirements earlier in the study process and thereby improve data quality and reduce rework.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console or Advarra EDC. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

Monitoring findings (i.e. eligibility errors, dosing errors, delay in serious adverse event reporting including SAE follow-up documentation, trends noted in deviations, delay in data entry, delay in query response) that are not resolved after discussion between the monitor, PI and/or study team may be escalated to the DSMC chair. The DSMC chair may reach out to the PI or request a written corrective action plan. Follow-up monitoring may be requested. Failure of the PI to address monitoring findings may result in protocol suspension.

Quality Assurance Audit Program

HCCC's Clinical Protocol and Data Management (CPDM) efforts are managed through Clinical Research Services (CRS) of HCCC through two related components - The Clinical Trials Support Office (CTSO) and Data and Safety Monitoring (DSM). These components are critical shared resources that support clinical cancer research including treatment, non-treatment interventional and non-interventional studies conducted by members of the HCCC. They encompass clinical research, regulatory, and data and safety monitoring and include investigator-initiated trials, NCTN trials, consortium trials, and industry sponsored trials.

To help ensure quality assurance, all CRS managed trials are subject to quality assurance audits. HCCC periodically selects and audits regulatory and/or subject documents to ensure HCCC monitoring standards are met. HCCC conducts these reviews for staff education, quality assurance and

improvement, as well as for compliance with the Data and Safety Monitoring Plan and relevant CRS Standard Operating Procedures.

The goals of the quality assurance auditing process are:

- To ensure ongoing clinical protocol compliance with IRB guidelines, FDA regulations, GCP guidelines and HCCC policies and procedures
- To educate clinical research staff to promote greater awareness and understanding of policies, procedures, and objectives, and to increase efficiency and consistency across trials
- To identify system changes needed within the HCCC to ensure quality improvement

All HCCC protocols are eligible for audit; however, priority is given to the following:

- Protocols not subject to frequent external auditing and monitoring, such as HCCC investigator-initiated trials
- Protocols with new principal investigators and/or primary research coordinators

These internal audits are coordinated by the Quality Assurance (QA) Officer and performed by QA staff and/or senior investigators not involved with the trial and DSMC staff not involved in the routine monitoring of selected studies. Audits are scheduled on a quarterly basis, with follow up or ad hoc auditing occurring as needed. Trials are subject to audits after the first subject is accrued. The assigned auditor reviews records for a randomly selected percentage of the accrual.

A written report of all audit deviations will be completed by the assigned auditor and reviewed with the PI and primary research coordinator. Audit findings will be reviewed by the Medical Director of Clinical Research Services and communicated to the DSMC. For any major deviations and/or multiple minor deviations, the QA Officer will issue a letter to the PI and request a written corrective action plan. Follow-up audits may be requested for protocols with multiple major deviations. Failure of the PI to adequately address protocol deviations may result in protocol suspension or termination.

Appendix 1

Template for Trial-Specific Data and Safety Monitoring Plan

Note for protocol writers/submitters: A complete protocol and data and safety monitoring plan (DSMP) includes specific information. Please carefully review the below template and directions prior to submission to help ensure timely review of the protocol.

1. All investigator-initiated protocols must identify the following information on the cover page:
   - IRB#
   - Protocol Title
   - Principal Investigator
   - Sub-Investigator(s)
   - Biostatistician(s)
   - Consultant(s)

2. All investigator-initiated protocols must include the following information within the protocol:
   - Subject inclusion criteria
   - Subject exclusion criteria
   - Stopping rules (subject and study)
   - Subject risks
   - Expected toxicities

3. The below DSMP template may be attached as an appendix to the protocol or incorporated into the body of the protocol. In either case, the same information must be included.

Template directions in blue text should be deleted prior to protocol submission.

Optional text in red should be edited or deleted prior to protocol submission.

Type of Clinical Trial:

- ❑ Investigator-initiated (UI/HCCC)
- ❑ Investigator-initiated, participating site
- ❑ Pilot study
- ❑ Phase I
- ❑ Phase I/II
- ❑ Phase II
- ❑ Phase III
- ❑ Compassionate-use/Expanded Access
- ❑ Interventional Treatment
- ❑ Interventional Non-Treatment
- ❑ Non-Interventional

Study risk-level:

- ❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
- ❑ Level 2—risk of death* <1% or any adverse event 1% – 5%
- ❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%
- ❑ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%
- ❑ Drugs being used on a "compassionate" basis

***** *Risk of death" refers specifically to 100-day treatment-related mortality*

Reporting and Monitoring Requirements:

All institutional investigator-initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, consent process documentation, eligibility, protocol compliance, and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Register all subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events and Serious Adverse Events
- Document protocol deviations
- Provide an annual progress report to the DSMC via OnCore or Advarra EDC data export

Select monitoring strategy based on risk-level (delete others):

Risk Level 1

Non-physical, non-interventional studies with a low risk of morbidity or death,* (<1% of death or any adverse event), e.g. observational, epidemiologic, laboratory use of left over samples from clinically indicated procedures,

and

Physical, non-interventional studies with a low risk of morbidity or death, * (<1% of death or any adverse event), e.g. behavioral surveys and questionnaires, music therapy, coping strategy assessment, nutrition assessment, healing touch studies, imaging (not using sedation), EKGs and gait assessments.

Study Safety Review

The PI or designated study personnel will review all study data for completeness

Risk Level 2

Interventional trials with a risk of death* (<1% or any adverse event 1% – 5%), e.g. behavioral interventions, nutritional therapies, low risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin or muscle biopsy, nasal wash, lumbar puncture, bone marrow biopsy, imaging requiring sedation), as well as therapeutic trials involving agents with known safety profiles already licensed for the indication and age group. Most disease-prevention trials will be considered at least a Risk Level 2.

Study Safety Review

The PI or designated study personnel will review all study data for completeness

Additional Reporting Requirements

- **A scanned copy of the completed eligibility checklist, with supporting source documents and PI signature, signed consent and documentation of consent process will be attached in OnCore for review by the DSMC monitor (Note: this is required if the protocol includes an eligibility checklist OR if required by PRMC/DSMC/IRB)]**
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and or DSMC monitoring staff for review.

Risk Level 3

Interventional treatment and non-treatment trials with a risk of death* (1% – 5% or grade 4 – 5 SAE 1% – 5%), e.g. moderate risk procedures Phase I or II clinical trials with available safety data in humans, studies treating subjects with placebo for a recognized disease, and trials with risk of radiation exposure.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore or Advarra EDC) and communicate with the PI at least annually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Identify critical data and processes

"Critical data" are defined as those data points that directly support the trial's primary objectives, safety endpoints, eligibility criteria, and protocol-mandated assessments. "Critical processes" are those operational activities that must be performed consistently and accurately to protect participants and ensure reliable study conduct.

At minimum, the following areas will be assessed to determine criticality:

1. **Eligibility Criteria**
   Verification of inclusion and exclusion criteria that directly impact participant safety or the interpretability of the study results.
2. **Informed Consent Process**
   Documentation that consent is obtained appropriately, using the current IRB-approved form, prior to study procedures, and includes proper comprehension and voluntariness checks.
3. **Safety Assessments and Adverse Event Reporting**
   Accurate and timely collection, grading, attribution, and reporting of adverse events, serious adverse events, and unanticipated problems.
4. **Primary and Key Secondary Outcome Measures**
   Correct and consistent measurement, documentation, and timing of endpoints that support the scientific validity of the study.
5. **Protocol-Required Procedures and Timing**
   Execution of essential study procedures, including laboratory assessments, imaging, treatment administration, investigational product management, and data entry within protocol-specified time windows.
6. **Data Accuracy and Source Documentation**
   Verification that data entered into the case report forms accurately reflect source documentation, especially for safety events, dosing, eligibility, and primary endpoint data.
7. **Investigational Product Accountability (if applicable)**
   Appropriate receipt, storage, preparation, dispensing, and reconciliation of investigational product.

The DSMP will prioritize monitoring of these critical data and processes. Adjustments to the criticality assessment will be made as needed throughout the study life cycle based on protocol amendments, unexpected safety trends, or feasibility considerations.

<u>Additional Reporting Requirements</u>

- A scanned copy of the completed eligibility checklist, with supporting source documentation and PI signature, signed consent document and documentation of consent will be attached in OnCore for ongoing review by DSMC staff.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to DSMC Chair/acting Chair or DSMC monitoring staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum once per year. Monitoring may be done more frequently depending on the protocol, risks to

subjects, reported serious/adverse events, patient population and accrual rate. A minimum of 25% of subject records will be monitored for the entire study.

Monitoring will involve the following:

- review eligibility of patients accrued to the study,
- check for the presence of a signed informed consent and documentation of consent,
- review adherence to treatment plan, including Investigational Product (IP) orders, drug doses dose reductions and/or treatment holds, if indicated,
- determine compliance with protocol's study plan, including assessment of primary and key secondary endpoint data,
- review whether deviations from the protocol are recorded and reported in OnCore, the IRB of record and external regulatory agencies as applicable,
- determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
- compare accuracy, adequacy, completeness, and timeliness of data collection in the research record and EDC data entry with the primary source documents,
- review quality of source documentation to ensure that records are attributable, legible, contemporaneous, original, accurate, and complete,
- review of possible dose limiting toxicities (DLTs),
- determine whether patient follow-up requirements are met,
- review investigational drug processing and documentation,
- assess cumulative AE/SAE reports for trends and compare to study stopping rules,
- review of regulatory documents

Risk Level 4

Interventional treatment trials involving investigational agents or devices with a risk of death* (>5% or grade 4 – 5 SAE >5%), e.g. all investigator initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore or Advarra EDC) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Additional Reporting Requirements:

- A copy of the completed eligibility checklist, with supporting source documentation and PI signature, signed consent document and documentation of consent process will be attached in OnCore and/or made available for ongoing review by DSMC staff.

- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. Records for a minimum of 25% of subjects will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - check for the presence of a signed informed consent and documentation of consent process,
  - review adherence to treatment plan, including Investigational Product (IP) orders, drug doses dose reductions and/or treatment holds, if indicated,
  - determine compliance with protocol's study plan, including assessment of primary and key secondary endpoint data,
  - review whether deviations from the protocol are recorded and reported in OnCore, the IRB of record and external regulatory agencies as applicable,
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy adequacy, completeness, and timeliness of data collection in the research record with the primary source documents,
  - review quality of source documentation to ensure that records are attributable, legible, contemporaneous, original, accurate, and complete,
  - review of possible dose limiting toxicities (DLTs),
  - determine whether patient follow-up requirements are met,
  - review investigational drug processing and documentation,
  - assess cumulative AE/SAE reports for trends and compare to study stopping rules,
  - review of regulatory documents

Routine Adverse Event Reporting

For non-serious Adverse Events, documentation must begin from the first day of study treatment and typically continue through the 30-day follow-up period after treatment is discontinued **[or the specified time point as defined in the protocol. Some protocols may require different timelines for AE reporting].**

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Terminology Criteria for Adverse Events (CTCAE), http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htmonset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Serious Adverse Event Reporting

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event. Updates on the event should be recorded weekly in OnCore until resolution. The final SAE report must be completed in OnCore no later than 7 (seven) days from the date the SAE is resolved.

A DSMC monitor will review IIT SAEs reported in OnCore to determine if the SAE is documented and reported accurately and in a timely matter. The information will be source verified.

An adverse event is considered **serious** if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

FDA Reporting Requirements (for Sponsor-Investigators) [remove entire section if not applicable]

[The following reporting requirements should be included in the DSMP of investigator-initiated trials for which the PI holds an Investigational New Drug Application (IND)]

It is the responsibility of the IND sponsor-investigator to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32. This responsibility includes providing an annual IND report to the FDA.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The type of report (initial or follow-up) should be checked in the respective boxes on Forms 3500A and 1571. See Instructions for completing Form 3500A. Please note all instance of UIHC, location, and faculty / staff should be redacted from supporting documentation and the 3500A.

The submission must be identified as:

- "IND safety report" for 15-day reports, or
- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

For detailed explanation of the above definitions, requirements, and procedures related to IND application safety reports and the responsibilities of IND applications sponsors with regard to such reporting, refer to Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (PDF - 227KB)

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known (grading the event per CTCAE)
- Supportive laboratory results and diagnostics

Sponsor-Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Protocol Deviation and Violation Monitoring

Definition
A protocol deviation is any departure from the approved study procedures, requirements, or regulations. Deviations are categorized as either:

- **Major deviations:** deviations that may affect participant safety, rights, or data integrity.
- **Minor deviations:** administrative or technical departures that do not affect safety, rights, or integrity.

Reporting Requirements

- Investigators must document and report all protocol deviations in the clinical trial management system (OnCore) within 7 **business days** of discovery.
- Major deviations/violations must also be reported to the IRB via a Reportable Event Form (REF) within 10 working days of the PI becoming aware of the event.
- The PI is responsible for implementing corrective and preventive actions (CAPA) for all major deviations.

DSMC Monitoring

- DSMC Monitors/Auditors will review deviations during routine monitoring visits and annual reviews.

- The DSMC will evaluate the frequency and impact of deviations, with attention to participant safety, protocol compliance, and trial integrity.
- Major deviations will be escalated to the DSMC Chair and, if warranted, discussed at a convened DSMC meeting.

Corrective Action

- Investigators and study teams must provide corrective action plans for major deviations.
- DSMC Monitors will verify implementation of corrective actions at subsequent monitoring reviews.

Documentation

- All deviation monitoring, findings, and DSMC determinations will be documented in the DSMC monitoring report and stored in OnCore..
-

Data Monitoring and Management **[This section applies to all risk levels]**

Subject Registration

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Each subject registration includes the following:

- The subject's IRB approved (version date) consent form and the date of their consent.
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

All subject registration information is expected to be entered into OnCore within **2 (two) business days** after the subject's study visit.

Subject Data

For HCCC investigator-initiated trials, research staff are responsible for entering subject study data (data collection) into OnCore electronic case report forms (eCRFs). These eCRFs must be approved by the PI and statistician prior to study activation to ensure sufficient and necessary data acquisition. All information entered into eCRFs will be traceable to the source documents which are generally maintained in the subject's file.

eCRF data entry needs to be timely and should be entered into OnCore as soon as possible but no later than **14 (fourteen) business days** after the subject's visit, including adverse events, tumor measurements, administration of study medication, concomitant medications, labs, and vitals. Physical exam assessments must be entered no later than **14 (fourteen) business days** following completion of the physician's clinic note in the medical record.

Timely data entry facilitates remote monitoring of data, allows the data to progress appropriately through the data cleaning process, and helps prevent a backlog of data queries.

Forms Monitoring

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all data are entered completely, accurately, and within time requirements outlined above. The assigned DSMC monitor will coordinate and complete the data monitoring review. When the time comes to monitor a study (based on patient accrual and assigned risk level of trial) the monitor arranges for a selection of cases to be reviewed from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries via OnCore (linked to the eCRF) to resolve missing, incomplete, and/or incorrect information. A member of the research team is expected to respond to these monitoring queries within **14 (fourteen) business days.**

The monitoring process can often identify misunderstandings or deficiencies in the written, research protocol requirements earlier in the study process and thereby improve data quality and reduce rework.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

Appendix 2

Multi-center Guidelines

[Include this section in the protocol specific DSMP for studies in which the University of Iowa is the lead site of a multi-site investigator-initiated trial].

Mission Cancer + Blood, Iowa Health Care is considered a participating UI Health Care site under the Appendix 2 multi-center guidelines. All protocols involving Mission must meet HCCC DSMP requirements, including OnCore registration, SAE reporting, data monitoring, and annual audits.

Trial Management

Data and Safety Monitoring Plan (DSMP)
The study will be conducted in accordance with the University of Iowa Holden Comprehensive Cancer Center's (HCCC) DSMP.

University of Iowa Principal Investigator Responsibilities

- As the lead site PI, the University of Iowa PI will be the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies. The PI is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the lead site PI. Any protocol modifications that may impact the statistical analysis plan of the protocol (e.g. study objectives, endpoints, or sample size calculations) must also be reviewed and signed of on by the lead site's statistician prior to IRB submission. There will be only one version of the protocol, and each participating institution will use that document. The lead site PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The University of Iowa PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the lead site PI.
- The University of Iowa PI is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The University of Iowa PI will be responsible for the review of and timely submission of data for study analysis.

HCCC Data and Safety Monitoring Committee

The DSMC will review the following:

- Serious adverse event summary report
- Monitoring and audit findings
- Data related to stopping/decision rules described in study design
- Protocol deviations

The HCCC DSMC will review aggregate safety data annually. Documentation of DSMC reviews will be provided to the lead site PI. Issues of immediate concern by the DSMC will be brought to the attention of the lead site PI and other regulatory bodies as appropriate.

Data Handling and Record Keeping

Data Management

Data will be collected through HCCC's Clinical Trial Management System (CTMS), OnCore. HCCC DSMC personnel will coordinate and manage data for quality control, assurance, and integrity. All data will be collected and entered into the CTMS by study site personnel from participating institutions.

Data Quality Oversight Activities

Remote monitoring by HCCC DSMC

Remote validation of eCRF data will be completed on a continual basis throughout the life cycle of the study by HCCC. A summary report of validation findings together with any queries resulting from manual review of the eCRFs will be generated for each participating site and transmitted to the site. Corrections will be made by the study site personnel.

Participating site personnel are responsible for uploading signed consent documents and a copy of the completed eligibility checklist, with screening information and PI signature, for each subject in OnCore for ongoing review by HCCC DSMC staff. Additional source documentation may be required to be uploaded in OnCore for remote monitoring.