Module V: Study Conduction

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Elements of Study Conduction

- Investigator Responsibilities
Investigator Responsibilities

When a Principal Investigator signs a 1572 he/she makes the following legal commitments to the FDA:

- **Personally** conduct or supervise investigation
- **Follow the protocol**
- Ensure all persons assisting in study are *adequately trained* and *informed* of their obligations
- **Inform subjects** that drugs are being used for investigational purposes
- Ensure *informed consent* (21 CFR Part 50) and **IRB review, approval and reporting** (21 CFR Part 56)
- Report **adverse events** to the sponsor (21 CFR 312.64)
- Maintain **adequate** and **accurate records** and make them available for inspection in accordance with 21 CFR 312.68
- **Ensure** initial and continuing review by an IRB and report **all** changes to research and unanticipated problems involving risks to subjects, no changes made without IRB approval except where necessary to eliminate immediate hazards
- **Comply** with other requirements in **21 CFR 312**
Investigator Responsibilities:
21 CFR 312 highlights

• Record keeping and retention (21 CFR 312.62)
  • Maintaining adequate records of drug disposition
  • Maintain accurate case histories that record all observations
  • Maintain other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation

• Safety reports (21 CFR 312.63)
  • Promptly report any adverse event that may reasonably be regarded as caused by, or probably caused by, the drug (err on the side of reporting)
  • Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
Investigator Responsibilities:

✓ Obtaining informed consent **prior to the performance of any study related procedures** including **documentation** in the subject’s research chart that written informed consent was obtained prior to the performance of any study related procedures

✓ **Ensuring** the informed consent document was approved by the IRB and that the **correct** version is being used

✓ **Complying with the IRB approved protocol** (regardless of sponsor). If change needed, amend protocol, submit to IRB

✓ Medically **supervising** the conduct of the clinical trial

✓ Maintaining **accurate** patient records and CRFs

✓ Ensuring **adequate reporting** of AEs, SAEs, and all other reportable events required by the regulatory oversight bodies
Investigator Responsibilities

- **Good News**: Clinical investigators are in charge
- **Bad News**: Clinical investigators are in charge and they are held accountable
- FDA regulations permit sponsors to delegate their responsibilities to Contract Research Organizations (CROs) but **do not permit clinical investigators to delegate their general responsibilities** to CROs or site management organizations, subinvestigators, or study staff
- **What can happen if noncompliant?**
  - Penalties for significant noncompliance
  - Warning Letters (posted on FDA website)
  - Disqualifications/Restrictions/Debarments in conduction of FDA regulated research (posted on FDA website)
  - Criminal prosecutions/prison/fines
Investigator Responsibilities:
Common mistakes/Risk factors for non-compliance

• Inadequate supervision and training of study staff
• Insufficient investigator involvement in study conduct
• Inappropriate delegation of study tasks to unqualified persons
• Failure to adequately protect study subjects
• Overworked investigator and study staff (e.g. too many subjects, complex study with large data collection, too many concurrent studies)

Guidance document outlining FDA expectations for study oversight and for protecting the rights, safety, and welfare of study subjects
Understanding the Difference between Clinical Practice and Clinical Research

**Clinical Practice:** Clinicians treat individual patients using standard treatment strategies that in his or her opinion are best for the patient.

**Clinical Research:** As an investigator conducting a clinical research study, the clinician is obligated to follow the study protocol that describes exactly how assessments and interventions must be carried out to ensure consistency across all study sites and participants.

Take the Hat Test: A patient presents with an ANC value of 900 mm$^3$.

- **Clinical Practice Hat:** the clinician would most likely treat the patient.
- **Clinical Research Hat:** the investigator cannot because the protocol treatment criteria states the ANC must be $\geq 1,000$ mm$^3$ to treat.
- The trick is to remember which hat you are wearing!
Elements of Study Conduction

- Investigator Responsibilities
- Subject Identification/Screening
Subject Identification/Screening: Initial Screening

- Potential study subjects are often identified by clinicians or their staff based on specific information regarding the patient’s disease and current disease status.

- Additionally, potential subjects or their primary physicians may inquire about a particular research study based on information they received from a public website search or from other sources.

- You **can** identify or “screen” potential subjects for appropriateness of participation in a given study based on the study’s major eligibility criteria (e.g. has specified disease-type and is within required age-range for participation).

- You **cannot** perform any screening procedures (e.g. blood tests, scans, etc.) for determining study eligibility prior to obtaining Informed Consent with potential subjects.
Pre-Study Screening and Eligibility

Screening Tests Prior to Study Enrollment

- Informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research

- While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out).

- Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, (such as for diagnosis or treatment of a disease or medical condition) may be performed and the results subsequently used for determining study eligibility without first obtaining consent. However, informed consent must be obtained prior to initiation of any clinical screening procedures that is performed solely for the purpose of determining eligibility for research.
Elements of Study Conduction

• Investigator Responsibilities
• Subject Identification/Screening
• Informed Consent Form/Process
Informed Consent Form/Process: Definitions

- **Informed Consent Document or Form (ICD/ICF)** - a document that describes the rights of participants in a clinical trial and includes details about the study, including its purpose, duration, required tests and procedures, potential risks and benefits, costs, and subject rights.

- **Informed Consent Process (ICP)** - an *ongoing* process for which the goal is to provide sufficient information to the potential subject regarding the study so that he or she can make an informed decision as to whether or not to participate in the research. It is the responsibility of the investigator (or the person responsible for obtaining consent) to present all information (both verbal and written) in a clear and comprehensive manner in order to maximize the potential subject’s understanding.
Informed Consent Form/Process: Informed Consent Form (ICF)

There are 8 required elements in an ICF, as mandated by the Code of Federal Regulations (CFR):

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental or investigational

2. A description of any reasonably foreseeable risks or discomforts to the subject

3. A description of any benefits to the subject or to others which may reasonably be expected from the research

4. A disclosure of appropriate alternative procedures or treatment, if any, that might be advantageous to the subject

5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and notes the possibility that the Food and Drug Administration may inspect the records
Informed Consent Form/Process: Informed Consent Form (ICF)

8 Required elements continued:

6. For research involving more than minimal risk, an explanation as to whether any compensation will be available if injury occurs and, if so, what it consist of, or where further information may be obtained

7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

*Some of these elements are required to be written verbatim per the IRB
Informed Consent Form/Process:
ICF - 7 Additional Required Elements

One or more of the following 6 additional elements may also be required in the ICF:

1. A statement that the particular treatment or procedure may involve **unforeseeable risks** to the subject (or to the embryo or fetus, if the subject is or may become pregnant)

2. Anticipated circumstances under which the subject's participation may be **terminated by the investigator** without regard to the subject's consent

3. Any **additional costs** to the subject that may result from participation in the research

4. The consequences of a subject's decision to **withdraw** from the research and procedures for orderly termination of participation by the subject

5. A statement that **significant new findings** developed during the course of the research which may relate to the subject's willingness to continue participation **will be provided to the subject**

6. The **approximate number of subjects** involved in the study
7. A statement that information regarding the specific clinical trial will be entered into ClinicalTrials.gov, a clinical trial registry database maintained by the NIH/NLM.

- Required for applicable clinical trials initiated on or after March 7, 2012
- Applicable clinical trial - those trials that are controlled clinical investigations, other than Phase I, of a drug subject to FDA regulation.

- The following statement must be reproduced word-for-word in ICFs for all applicable clinical trials:

  “A description of this clinical trial will be available on http://ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”

FDA guidance: (in PI Toolkit)
In order to consent a potential subject regarding a specific study, you must first:

- Read the protocol and make certain that you understand all aspects of the research trial. Review the study parameters and the study schedule so you can answer questions easily.

- Read through the consent form BEFORE presenting it to a subject so that you have a clear understanding of the study without having to fumble through the pages to find specific information.

- Make certain to bring 2 copies of the ICF so you can give the potential subject one and you can have one to reference as you go through it with them.
Informed Consent Form/Process: Informed Consent Process (ICP)

Remember, the ICP is an ongoing process

- Discussions with potential subjects should take place in a private location (exam room vs waiting room) to protect the potential subject’s confidentiality and the individual should be provided sufficient time to consider participation.

- Review each section of the consent document with the subject, taking time to explain significant or difficult points about the research or participation. You must make certain to go over the eight required elements of the ICF with the potential subject.

- Answer questions that the participant and/or family members may have. If you do not know the answer, speak with the investigator or another member of the research team who is familiar with the protocol.

- When speaking to the participant, remind them that what you are discussing is in the ICF and they can refer back to it as often as needed.
After the informed consent discussion, but before the potential subject signs the consent form, it may be appropriate to encourage him/her to take the consent form home and discuss the decision to participate with family or friends.

After the potential subject has had ample time to review the consent form and ask questions, assess the subject’s understanding about the material presented, including the nature of the study and voluntary participation. This assessment may be done by asking open ended questions.

- For example, ask the subject to explain the purpose of the study in his or her own words. Allow enough time during the conversation for the potential subject to ask questions, and encourage him/her to do so.
Informed Consent Form/Process:

ICP - Signing the ICF:

When all of the subject’s questions have been answered and you feel they fully understand what their participation in the trial requires and they have decided to participate in the study:

• The subject must sign and date the ICF on the line for “Subject Signature” and “Date”

• There must also be a signature and date for “Person Obtaining Consent” (POC), even in the absence of a line! (ICH GCP)

    !!!! These two dates MUST match !!!!

• Subject must sign and date the HIPAA, if the HIPAA is a separate document and not combined with the consent form

• A copy of the signed consent forms must be made and given to the subject

• Note: Some industry sponsored trials require that subjects initial each page of the consent form

• If there are multiple consent forms for a given trial, the subject must sign and date each consent form (and POC sign/date as well) i.e. correlative study

• DOCUMENT the ICP in the research chart

• Original signed consent(s) must be kept in the subject’s research chart
Informed Consent Form/Process:
ICP Documentation

- The ICP must be documented thoroughly in the research chart in either a Progress Note or in the HealthLink record.

- Sample documentation for ICP:

  “Pt came in today (date) to discuss ____ study. Consent was reviewed in its entirety with pt and husband, including potential risks and side effects, alternatives to treatment, study schedule, confidentiality issues, etc. Pt asked appropriate questions that were answered to her satisfaction. Pt. expressed understanding and agreed to participate. Pt. declined participation in optional sub-study due to work schedule. Pt. signed and dated ICF and HIPAA as did study coordinator. Pt. received a copy of the signed documents.”
Informed Consent Form/Process:

ICP - Telephone Consenting

Obtaining IC over the phone is **not** Best Practice, and should be done only when it is a hardship for the pt to return to clinic for the ICP (i.e. lives a distance away) after having taken the consent home to discuss with family

How it should be done:

- Potential subject contacts you (or vice-versa if agreed to) to further discuss potential participation

- Review the consent with the potential subject (this is in addition to having gone through the consent with the subject in clinic)

- Answer any and all questions or concerns the potential subject may have and ensure they fully understand the study

- If the potential subject has decided to participate, they must sign and date the ICF and HIPAA and send it back to the clinic either by mail, fax, or scanned email

- The consent form then must be signed and dated by the person obtaining consent immediately upon receipt

- Both subject and person obtaining consent must resign and re-date the forms when the subject returns to clinic. Remember- **THE DATES OF SIGNATURES MUST MATCH!**

- Under no circumstances may any research procedures be performed before the study group receives the signed and dated forms and co-signs and dates them. This **all** must be documented fully in the research chart
Informed Consent Form/Process: ICP - Correlative Studies

• Some studies have optional correlative portions (e.g. sample and tissue banking) in them where subjects need to indicate whether they consent to participate in these optional portions of the protocol, usually by circling Y or N or initialing.

• For these optional portions, remind participants they can still participate in the main study even if they choose not to consent to the correlative portion.

• If the correlative section has a separate consent form, ensure that the subject and consenter signs and dates those consent forms as well. Copies of the signed consents need to be made and provided to the subject.

• However, there are some studies that have correlative components which are not optional (if they do not want to participate in the correlative portion, they cannot participate in the main study) – Make certain you know before hand whether or not a particular study’s correlative portion is optional or not for participation in the study.

• Regulatory Specialists are responsible for letting the IRB know if there are correlative portions.
Informed Consent Form/Process:

ICP - HIPAA Research Authorization Form

- The federal law known as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its regulations (“Privacy Rule”) require researchers to obtain written authorization from research participants before using or disclosing the participants’ individually identifiable health information (Protected Health Information or PHI) for research purposes.

- In addition to the Informed Consent Form (ICF), study participants must be given a HIPAA research authorization form that details the “covered entities” that will have access to their PHI.

- The HIPAA form must be signed and dated along with the ICF by the study participant and person obtaining consent.

- A copy of the signed and dated HIPAA form should be provided to the research subject.
Informed Consent Form/Process: ICP - Re-Consenting

- Re-consenting occurs when the IRB or coordinating center for a study decides that the addition of new information (e.g. risks, additional tests) needs to be shared with study subjects that are already on study.

- Take as much time and care in explaining the change(s) as when you initially consented these participants, to make certain the subject understands and can make an informed decision as to whether or not to continue in the study.

- The subject and consenter must sign and date the new consent. A copy of the newly signed consent must be provided to the subject.

- The subject could decline further participation based on the changes, as they can at any time during participation.
Informed Consent Form/Process:
Re-Consenting ICP Documentation

• The re-consenting ICP must be documented thoroughly in the research chart in either a Progress Note or in the HealthLink record

• Example of re-consenting ICP documentation:
“Pt came in today (date) to continue participation in _____ study. Needed to re-consent the subject prior to treatment due to change in consent. The changes to the consent (specify: new risk information) was reviewed with pt and husband, Pt asked appropriate questions that were answered to her satisfaction. Pt. expressed understanding and agreed to continue to participate in the study. Pt. signed and dated new ICF as did the study coordinator. Pt. received a copy of the newly signed ICF.”
Elements of Study Conduction

- Investigator Responsibilities
- Subject Identification/Screening
- Informed Consent Form/Process
- Eligibility Determination & Subject Registration
Eligibility Determination & Subject Registration:

Eligibility

• Once the subject has signed the consent form, you can now proceed to determine whether or not he/she is eligible to participate in the study.

• Eligibility is determined by following the Inclusion/Exclusion criteria in the Protocol.

• Pts must meet **ALL** eligibility requirements as stated in the protocol. **No exceptions.**

• UWCCC policy dictates: **No eligibility waivers**
Eligibility Determination: Considerations

- Eligibility Checklist - PI must sign and date the eligibility checklist prior to the subject being registered to the study – this is not only so that the eligibility checklist can be considered source documentation but more importantly to ensure that the PI has confirmed the subject's eligibility.

- Prior test results can be used for inclusion (now that consent has been obtained) if they meet the specified timeline (i.e. per the protocol, bone scan must be obtained within 4 weeks of registration).

- Specific timelines must be met for all eligibility criteria (i.e. per the protocol, labs must be obtained within 2 weeks of registration).

- You cannot “make” the pt. eligible for the study. If their lab results are not within the range for eligibility, they are ineligible. You can have them come back at a later date to retest, but you cannot try to manipulate their lab values for eligibility into a study (i.e. treat with steroids to effect lab values) unless it is part of their clinical care.
Eligibility Determination & Subject Registration:
Eligibility

• Eligibility Checklist- PI must sign and date the eligibility checklist prior to the pt. being registered to the study – this is to ensure that they confirmed the pt.'s eligibility

• Make certain that the specific timelines for eligibility criteria are met (i.e. per the protocol, labs must be drawn within 2 weeks of starting on study)

• Cannot “make” the pt. eligible for the study. If their lab results are not within the range for eligibility, they are ineligible. You can have them come back at a later date to retest, but you cannot try to manipulate their lab values for eligibility into a study (i.e. treat to effect lab values) unless it is part of their clinical care.
MEMORANDUM

To: UWCCC and Wisconsin Oncology Network Principal Investigators  
From: Brad Kahl, MD, Associate Director for Clinical Research  
Date: March 6, 2009  
RE: Eligibility Waivers

This Memorandum is to serve as a reminder of the UWCCC/WON Policy regarding eligibility criteria waivers for subject participation on UWCCC/WON studies.

- Under no circumstances can a UWCCC/WON study chair approve an eligibility override.
- If any eligibility requirements in the protocol are ambiguous or unclear or if there is a question where eligibility evaluation requires subjective interpretation that is not strictly detailed in the protocol, the study chair may provide clarification. In difficult cases, consultation with the Associate Director for Clinical Research is encouraged. The study chair should then consider developing a protocol amendment that further clarifies the eligibility criteria in question. Documentation of the interpretation of eligibility and any discussions related to this interpretation needs to be included in the case file.
- Entry to study will be denied if any quantitative pre-study data is outside the limits defined in the eligibility criteria of the protocol. No overrides are permitted in this circumstance.
- These guidelines apply to cooperative group, investigator initiated, and industry sponsored trials.
Eligibility Determination & Subject Registration: Subject Registration/Enrollment

• Once the subject has been consented and eligibility has been verified by the PI, that subject can be registered to the trial

• Each sponsor has a specific mechanism for registering a subject to a trial:
  • Industry or Cooperative Groups- Registration is usually completed via an electronic registration system or fax
  • Investigator-Initiated trials- Registration is completed via the UWCCC database, OnCore, in the subject console of the specific protocol

• Reference your protocol for instructions on how to register/enroll your study participants
Eligibility Determination & Subject Registration: Subject Registration/Enrollment

• Each registered subject is provided with a unique sequence # or subject ID

• Make certain to keep copies of all registration documentation in the research chart

• Regardless of study sponsor, all subjects are entered into the OnCore database
Eligibility Determination & Subject Registration: Treatment on a clinical trial

- Treatment must be administered strictly following the parameters laid out in the protocol
- It must be clear in the research chart what treatment regimen the individual subjects were assigned to (i.e. Arm A or B, randomization assignment, etc.)
- The study parameter (schedule) section of the protocol must be strictly adhered to, such that subjects receive all specified lab testing and procedures AND results are reviewed PRIOR to treatment.
  - If the pt. presents for treatment but their labs are not in range to treat (per protocol)- DO NOT TREAT- it is a protocol violation to do so
- If assigned dose requires alteration per the protocol, this must be clearly documented in the research chart. All dose reductions or delays must be clearly explained in the research chart
- Flow sheets must be present in the chart to show IV dosing administration, including the drug administered, the amounts administered and the start and end times.
- Oral drug dispensation must be clearly documented and must include the prescribed doses (i.e. copy of prescription). Pill diaries are not documentation of what was administered or prescribed to the pt.
Elements of Study Conduction

- Investigator Responsibilities
- Subject Identification/Screening
- Informed Consent Form/Process
- Eligibility Determination & Subject Registration
- Data Collection & Data Quality
To ensure the reliability of results of any clinical trial, ALL reported data must be:

- Complete
- Accurate
- Verifiable
Data Collection:
Source Documentation

• **Definition**: Source documentation represents the first time an observation or data point is recorded on a clinical trial subject. It is anything in a subject’s medical record or research chart from which data is drawn (i.e. procedures, physician notes, etc.)

• The foundation of all clinical studies
  
  • Confirms complete and accurate data collection
  
  • Shows evidence that the study was conducted not only according to the protocol but also ethically
  
  • “An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each subject” (CFR 312.62)

  “Without documentation, there is no data”

  “If it wasn’t written down, it wasn’t done”

  **Rule of thumb**: “Document, Document, Document, and when you’re done...Document some more”
Data Collection:

Source Documentation

Examples of actual source docs:

- Screening forms
- Medical records
- Nurse/ CRA visit notes, flowsheets, physical exam notes, checklists and AE lists
- Vitals
- Physician dictations
- Signed consent form(s)
- Medication dispensing records
- CT scans/ X-ray / MRI films and reports
- Laboratory, Pathology, and Surgery reports
- Treatment administration records (chemotherapy, radiation/radiotherapy records)
- Subject pill diaries (for oral medication)- must be signed by subject
- Eligibility checklist (considered source document if signed by physician prior to registration)
- Study specific worksheets
Data Collection:

Source Documentation

Required documentation in clinical research:

- Informed Consent Process- can use smart phrase, but must be in chart
- Medical history
- Eligibility criteria
- Progress notes from each visit
- Physical examinations
- Study medication administration and self-administered medication (pill diaries)
- Adverse Event Log with grading and attribution
- Justifications for dosing adjustments
- Lab/radiology results
- Phone calls/emails with subject
- Phone calls with study chair/coordinating center
- Sponsor Correspondence
- Documentation of reported noncompliance
- Subject study status- is subject on-study, off-study, off-treatment, in follow-up, etc.?
Data Collection: Source Documentation

Tips for Source Documentation

• Performance Status (PS) should be documented, but in its absence, it can be inferred from the MD dictation

• Each eligibility criteria MUST be found in source documentation (see above point)

• If subject is female of childbearing age, a pregnancy test must be run and the result MUST be in the chart before she can be treated. Note: this requirement may vary depending on the study

• Treatment delays and dose modifications MUST be clearly documented in the MD dictation and/or RN/CRA progress notes

• Source documentation cannot be created after the fact

• Notes To File (NTF) can be created to clarify specific information (i.e. why a subject came in for treatment outside of the study visit window specified in the protocol)
Data Collection:
Source Documentation

What Notes to File are:
• Identification of a problem that occurred during a clinical trial
• Procedural change identified to correct the problem to prevent reoccurrence

What Notes to File are not:
• A corrective action
• Helpful as an “after-the-fact memo”
• A replacement for reporting to oversight bodies
• A replacement for carrying out the appropriate corrective action
  • i.e. Subject did not indicate “yes” or “no” on optional sample collection.

NTF become a road map for an auditor to see all the mistakes made during the conduct of the protocol

Corrective action and the carrying out of that correction action should be what’s documented.

NTF should be kept a minimum- How? By following the protocol
Data Collection:
Case Report Forms (CRFs)

- **Definition**: Forms that are used to capture protocol-required data for submission (paper or electronic)

- CRFs standardize the collection of protocol-required data, allow for consistent reporting of data (across participating research sites) and increase efficiency in processing and analyzing data

- **EVERY** data item on a CRF **MUST** be verifiable in the subject’s medical record or research chart
Data Collection:
GCP CRFs

Tips for completing CRFs and source documentation

• To correct (or “amend”) an error, line through the error once and initial and date, then put the correct entry next to it

• Never use white out or correction fluid

• Use only black ink (no colored pens, markers, or pencils should ever be present on a CRF or in the research chart)

• Write legibly

• NEVER make stuff up!
  • If a procedure was not performed (i.e. obtaining weight and height), you must indicate in the research chart and on the CRF that it was not collected
Data Collection: Submitting CRFs

• Paper CRFs are completed and submitted to the sponsor by mail or fax. If CRFs are not carbon-copies, photocopies of all documents and forms should be made prior to submitting the originals to the sponsor. Copies are maintained in the research file.

• eCRFs are electronic case report forms and are entered directly into an electronic data capture system
  • A number of industry sponsors use eCRF data capture for their trials
    • In this case, the sponsor will usually provide a laptop to the research site specifically for protocol data entry
  • For Institutional trials, eCRFs are created and completed in OnCore, the UWCCC database.
Data Collection:

Data Integrity

The Role of the Study Coordinator in Ensuring Data Integrity:

• All CRFs should be reviewed for accuracy and completeness prior to submission:
  • Incomplete or discrepant data on CRFs will generate queries from coordinating site (whether it be industry, cooperative group or UWCCC)

• All CRFs should be completed and submitted in the time frame outlined by the study sponsor, and outlined in the protocol:
  • i.e. Within 48-72 business hours after each study visit
Data Collection:
Data Correction Forms (DCFs) aka. Queries

- Queries are sent to the research group when there is incomplete or discrepant data

- Queries from industry sponsors usually come in the form of a fax or email
- Queries from cooperative groups or from the UWCCC OnCore Support Team come in the form of an email

- Queries may request that the research team clarify or amend the data

- Queries should be resolved within no more than 10 days after receipt or specific timeframe outlined by the sponsor
Elements of Study Conduction

- Investigator Responsibilities
- Subject Identification/Screening
- Informed Consent Form/Process
- Eligibility Determination & Subject Registration
- Data Collection
- Adverse Events/Serious Adverse Events
Adverse Events (AEs)

• An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

• PI determines whether the AE is related to study treatment

• The AE is reported in the research chart and on CRFs
Serious Adverse Events (SAEs)

An SAE is any adverse drug experience resulting in any of the following outcomes:

1. Death
2. Life threatening adverse drug experience
3. In-patient hospitalization or prolongation of existing hospitalization
4. A persistent or significant disability or incapacity
5. A congenital abnormality or birth defect
6. Any other event that may jeopardize the subject or may require intervention to prevent the above outcomes

PI must determine attribution (relatedness), expectedness and seriousness (grade) of the event
AEs/SAEs:
Assessment and Reporting Tools

• **CTC / CTCAE**: Common Toxicity Criteria (for Adverse Events)
  - The CTC/CTCAE is a collection of standardized descriptions of AEs and the grading out of the severity of those events for oncology clinical trials with therapeutic interventions.
  - The CTC/CTCAE lists AE terms commonly encountered in oncology; assist in the recognition and severity grading of AEs; standardize reporting of AEs across groups and treatment modalities; supply guidelines for protocol eligibility, Dose Limiting Toxicity, Maximum Tolerated Dose and dose modification.

• **CAEPR**: Comprehensive Adverse Event and Potential Risks
  - The CAEPR is a complete list of reported and/or potential AEs associated with an agent under a CTEP Investigational New Drug (IND). These are often listed in the protocol for a specific agent, and are often updated when new risks become known.

• **SPEER**: Specific Protocol Exceptions to Expedited Reporting
  - The SPEER is a subset of AEs within the CAEPR which contains events that are considered expected. Report events that are > than grade listed.

• **AdEERS**: Adverse Event Expedited Reporting System
  - NCI's web-based system for submitting expedited reports for serious and/or unexpected events forwarded to designated recipients and the NCI for all trials using a NCI-sponsored investigational agent.

• **MedWatch**:
  - FDA system used for reporting SAEs for studies using commercial agents.
AEs/SAEs:

Recording & Reporting of AEs & SAEs

• All AEs and SAEs experienced by subjects participating in a clinical trial must be documented in the research chart.

• All AEs must be graded out (CTC/CTCAE) and assessed for expectedness and relatedness to the investigational drug.

• All SAEs must be reported to the sponsor, IRB (if it meets their reporting guidelines), and the Data Safety Monitoring Committee.

• It is the PI’s responsibility to assess and grade out each AE/SAE. It is not appropriate to delegate this responsibility to the Study Coordinator. This is a function that **must** be performed by the PI or the **Subinvestigator**.

• An AE log must be in the research chart tracking and grading AEs as they are reported. Each event must be signed and dated by the PI.

• AEs must be clearly graded. If a physician says “profuse diarrhea”, it **must** be assigned a grade in order to know if it meets criteria for reporting, as well as if it requires a dosing alteration.
AEs/SAEs:

Recording & Reporting of AEs & SAEs

• Adverse event collection and reporting is a routine part of every clinical trial.
• The first step is to identify the event using the CTC/CTCAE.
• The severity of the event should then be graded using the CTC/CTCAE criteria.
• This information and the adverse event reporting tables in each protocol, allows the investigator to determine whether an adverse event should be reported to the NCI as an expedited report (AdEERS) or a routine report
• Clinical investigators and ultimately the Principal Investigator (PI) have the primary responsibility for AE identification, documentation, grading, and assignment of attribution
• Reporting requirements differ for AEs and SAEs:
  • Routine AEs are reported on Case Report Forms
  • SAEs require expedited reporting using AdEERS or Medwatch reports
AEs/SAEs:

SAE Reporting Criteria

Seriousness

• The grade of an AE relates to the seriousness of an event for the purposes of regulatory reporting

• The CTC/CTCAE is used to identify the event and the grade of an event

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0
Published: May 28, 2009 (v4.02: Sept. 15, 2009)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf
AEs/SAEs:

AE and SAE Reporting

• The 3 main criteria that need to be assessed to determine reporting of an AE:
  
  - Severity
  
  - Expectedness
  
  - Attribution
AEs/SAEs:

SAE Reporting Criteria

**Grading**

Grade 0: No AE or within normal limits

Grade 1: Mild AE

Grade 2: Moderate AE

Grade 3: Severe and undesirable AE

Grade 4: Life-threatening or disabling AE

Grade 5: Fatal AE

Refer to your CTC/CTCAE for more in-depth definitions
Expectedness

Expected:
- The event is listed in the consent form as a known side effect/risk
- The event is listed on the SPEER at an expected grade

Unexpected:
- The event is NOT listed in the consent form as a known side effect/risk
- The event is NOT listed on the SPEER
AEs/SAEs: SAE Reporting Criteria

Attribution
-The determination of whether an AE is related to medical treatment or procedure
  • The PI must assign attribution for an adverse event after naming and grading of the event

**Unrelated**: The AE *is clearly NOT related* to the intervention

**Unlikely**: The AE *is doubtfully related* to the intervention

**Possible**: The AE *may be related* to the intervention

**Probable**: The AE *is likely related* to the intervention

**Definite**: The AE *is clearly related* to the intervention

*Note: The IRB requires reporting for “Probable” and “Definite” while the DSMC requires reporting for “Possible”, “Probable”, and “Definite”*
AEs/SAEs:

SAE Reporting

1. Identify the event using the CTC/CTCAE criteria

2. Assign grade (seriousness) of the event using the CTC/CTCAE criteria

3. Determine if the event meets SAE/expedited reporting requirement per the protocol by refer to the reporting tables in the protocol

6. All reported events must be reported via the routine reporting requirements defined by guidelines provided by sponsors, Cooperative Groups, and the UWCCC
The reporting of SAEs includes, but is not limited to:

- **Study Sponsor** (Industry, NCI, Cooperative Group)
  - Refer to the protocol document section dealing with Adverse Event reporting requirements
  - Refer to the Study Procedures Binder from the sponsor for industry trials

- **IRB**
  - Refer to the UW Health Sciences IRBs website at [http://kb.wisc.edu/hsirbs/](http://kb.wisc.edu/hsirbs/) for information concerning:
    - Adverse Event Reporting Guidelines and Decision guide
    - Serious Adverse Event Report Form
  - There are a number of IRBs being used by the UWCCC DOWGs, each with differing ways of reporting events. Examples include the UW Health Sciences IRB, WIRB and CIRB
    - External Sites should follow institutional guidelines for reporting events to their IRB

- **UWCCC Data And Safety Monitoring Committee (DSMC)**
  - All Serious Adverse Events must be reported to the UWCCC Data Safety Monitoring Committee (DSMC) via [saenotify@uwcarbone.wisc.edu](mailto:saenotify@uwcarbone.wisc.edu)

- **FDA** (if the UWCCC holds the IND)
AEs/SAEs:

SAE Reporting to UWCCC DSMC

• The UWCCC SAE SOP (uwccccc.wisc.edu.content/sop) describes in detail how to report SAEs to the UWCCC DSMC

• Highlights:
  • All SAEs are reported to the DSMC
  • All SAE reports are sent to the DSMC chair via the saenotify@uwcarbone.wisc.edu email address. Follow-up reports are required within 10 days
  • Instructions for affiliate sites and reporting criteria for SAEs is described in detail in the SAE SOP
  • All SAEs are recorded in the OnCore database in the subject console and a report is generated in OnCore containing the information that is entered. This is what is sent to the DSMC Chair
AEs/SAEs:

SAE Reporting

AdEERS

- NCI's web-based system for submitting expedited reports for serious and/or unexpected events forwarded to designated recipients and the NCI for all trials using a NCI-sponsored investigational agent (i.e. Cooperative Group trials)

- Log in to the AdEERS interactive web training:
  
Legacy tables: AdEERS Expedited Reporting Requirements for Adverse Events that occur within 30 Days¹ of the Last Dose of the Investigational Agent

### Phase 1 Trials

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected &amp; Expected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexpected</td>
<td>Not Required</td>
<td></td>
<td>Not Required</td>
<td></td>
<td>Not Required</td>
<td></td>
</tr>
<tr>
<td>Expected</td>
<td></td>
<td>Not Required</td>
<td></td>
<td>Not Required</td>
<td></td>
<td>Not Required</td>
</tr>
</tbody>
</table>

|                |          |         |         |         |         |               |
| Unrelated Unlikely |       | Not Required |    | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days |
| Possible Probable Definite |     | Not Required | 10 Calendar Days |     | 24-Hour; 5 Calendar Days | 24-Hour; 5 Calendar Days | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days |

1  Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 4 unexpected events
  - Grade 5 expected and unexpected events

2  Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004
### Legacy Tables: Expedited Reporting Requirements for Adverse Events that occur within 30 Days\(^1\) of the Last Dose of the Investigational Agent

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td></td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td>Probable</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

AdEERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

\(^2\) Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

\[\text{December 15, 2004}\]
**New Reporting tables (for trials approved after 3/28/2011)**

**Appendix 1: Expedited Reporting Requirements for NCI IND/IDE Agents**
(cont.)

### Phase 0 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). 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 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).

<table>
<thead>
<tr>
<th>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1 and 2 Timeframes</strong></td>
</tr>
<tr>
<td>10 Calendar Days</td>
</tr>
</tbody>
</table>

**Expedited AE reporting timelines are defined as:**

- **“24-Hour, 5 Calendar Days”** - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **“10 Calendar Days”** - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1. **Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention require reporting as follows:** Expedited 24-hour notification followed by complete report within 5 calendar days for ALL Grade 4 and 5 AEs and Grade 3 AEs with at least a possible attribution. **NOTE:** Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

2. For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded up to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.
Appendix 1: Expedited Reporting Requirements for NCI IND/IDE Agents (cont.)

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention 1, 2

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 and Grade 2 Timeframes</th>
<th>Grade 3-5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:
- "24-Hour, 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs
- Expedited 10 calendar day reports for:
  - Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

2For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded up to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

NOTE: Deaths clearly due to progressive disease should NOT be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

*NOTE:* Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.84)

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).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

**Expedited AE reporting timelines are defined as:**

- **24-Hour; 5 Calendar Days** - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

   - Expedited 24-hour notification followed by complete report within 5 calendar days for:
     - All Grade 4, and Grade 5 AE
   - Expedited 10 calendar day reports for:
     - Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
     - Grade 3 adverse events

2. For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded up to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

**NOTE:** Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).
Appendix 1: Expedited Reporting Requirements for NCI IND/IDE Agents (cont.)

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention\(^1\,2\)

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization</td>
<td></td>
<td>10 Calendar Days</td>
<td></td>
<td>24-Hour 5 Calendar Days</td>
</tr>
<tr>
<td>≥ 24 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization</td>
<td></td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
</tr>
<tr>
<td>≥ 24 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

**Expedited AE reporting timelines are defined as:**
- **"24-Hour, 5 Calendar Days"** - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **"10 Calendar Days"** - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

\(^1\)Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**
- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

\(^2\)For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded up to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

**NOTE:** Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).
# HS-IRB SAE reporting

## HS-IRBs Reporting and Submission Timeframes
**January 2013**

This table is a supplement other HS-IRBs guidance documents regarding the reporting of adverse events, noncompliance, unanticipated problem, and new information as well as changes of protocol and continuing reviews. This document is intended to assist study teams with understanding the different reporting and submission timeframes and is NOT comprehensive (e.g., personnel change timeframes are not described below). Study teams should refer to the appropriate policy and guidance documents for a complete description of what events need to be reported and when.

<table>
<thead>
<tr>
<th>Timeframes</th>
<th>Event/Submission</th>
<th>What to Submit</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Business Day: Studies Involving Drugs or Biologics</td>
<td>An event must be reported within 1 business day if it is:</td>
<td>Call or email the IRB chair and director.</td>
<td>- Reporting Requirements for Studies Involving Drugs or Biologics</td>
</tr>
<tr>
<td></td>
<td>- Probably caused by or associated with study participation; and</td>
<td></td>
<td>- Unanticipated Problems Reporting Decision Tree</td>
</tr>
<tr>
<td></td>
<td>- Unexpected; and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Immediately life-threatening or severely debilitating to current subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>or others not participating in the study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Business Day: Studies Involving Testing of Devices</td>
<td>An event must be reported within 1 business day if it is:</td>
<td>Call or email the IRB chair and director.</td>
<td>- Reporting Requirements for Studies Involving Investigational Devices</td>
</tr>
<tr>
<td></td>
<td>- Not previously identified in nature, severity, or frequency in IRB</td>
<td></td>
<td>- Unanticipated Problems Reporting Decision Tree</td>
</tr>
<tr>
<td></td>
<td>documentation (e.g., protocol, consent documents) OR relates to subjects’</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rights, welfare, or safety AND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Immediately life-threatening or severely debilitating to current subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Business Day: Noncompliance Requiring Intervention to Prevent Serious Harm to Subjects or Others</td>
<td>Noncompliance must be reported to the IRB within 1 business of discovery by the study team if intervention of any kind is required to prevent serious harm to subjects or others.</td>
<td>- Call or email the IRB director or chair.</td>
<td>Noncompliance Policy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- A report of noncompliance also should be submitted in ARROW.</td>
<td></td>
</tr>
</tbody>
</table>
# HS-IRB Reporting

## HS-IRBs Reporting and Submission Timeframes

**January 2013**

This table is a supplement to other HS-IRBs guidance documents regarding the reporting of adverse events, noncompliance, unanticipated problem, and new information as well as changes of protocol and continuing reviews. This document is intended to assist study teams with understanding the different reporting and submission timeframes and is NOT comprehensive (e.g., personnel change timeframes are not described below). Study teams should refer to the appropriate policy and guidance documents for a complete description of what events need to be reported and when.

<table>
<thead>
<tr>
<th>Timeframes</th>
<th>Event/Submission Type</th>
<th>What to Submit</th>
<th>Resources</th>
</tr>
</thead>
</table>
| 14 Business Days: Probably Caused By or Associated with Study Participation | An event must be reported within 14 business days if it is probably caused by or associated with study participation if it is:  
- Unexpected and suggests the research places subjects or others at greater risk of harm  
- Unexpected and will result in a change to any study documents and/or provision of new information to subjects or others  
- Not previously identified in nature, severity, or frequency in IRB documentation (e.g., protocol, consent document) OR relates to subjects’ rights, welfare, or safety | - If the event is unexpected and suggests the research places subjects or others at greater risk of harm, report as an unanticipated problem  
- If the event is unexpected and will result in a change to any study documents and/or provision of new information to subjects or others, report as new information | - Guidance on Reporting Unanticipated Problems  
- New Information Reporting Guidance  
- Unanticipated Problems Reporting Decision Tree |
HS- IRB Reporting

HS-IRBs Reporting and Submission Timeframes
January 2013

This table is a supplement other HS-IRBs guidance documents regarding the reporting of adverse events, noncompliance, unanticipated problem, and new information as well as changes of protocol and continuing reviews. This document is intended to assist study teams with understanding the different reporting and submission timeframes and is NOT comprehensive (e.g., personnel change timeframes are not described below). Study teams should refer to the appropriate policy and guidance documents for a complete description of what events need to be reported and when.

<table>
<thead>
<tr>
<th>Timeframes</th>
<th>Event/Submission Type</th>
<th>What to Submit</th>
<th>Resources</th>
</tr>
</thead>
</table>
| 14 Business Days: Probably Caused By or Associated with Study Participation | An event must reported within 14 business days if it is probably caused by or associated with study participation if it is:  
• Unexpected and suggests the research places subjects or others at greater risk of harm OR  
• Unexpected and will result in a change to any study documents and/or provision of new information to subjects or others OR  
• Not previously identified in nature, severity, or frequency in IRB documentation (e.g., protocol, consent document) OR relates to subjects’ rights, welfare, or safety | - If the event is unexpected and suggests the research places subjects or others at greater risk of harm, report as an unanticipated problem  
- If the event is unexpected and will result in a change to any study documents and/or provision of new information to subjects or others, report as new information | - [Guidance on Reporting Unanticipated Problems](#)  
- [New Information Reporting Guidance](#)  
- [Unanticipated Problems Reporting Decision Tree](#) |
Elements of Study Conduction

• Investigator Responsibilities
• Subject Identification/Screening
• Informed Consent Form/Process
• Eligibility Determination & Subject Registration
• Data Collection
• Adverse Events/Serious Adverse Events
• Toxicity Grading/Dose Modifications
Toxicity Grading/Dose Modifications

• Once an adverse event is graded for toxicity level utilizing the CTC/CTCAE, it can result in dose modifications to drug or radiation treatment

• Reference the protocol to determine if the event will result in:
  • **No modification**: Continue with same treatment dose
  • **Hold/Delay**: treatment held or omitted for a specified time frame
  • **Modification**: dose will be reduced or changed in some way to accommodate toxicity
  • **Termination**: subject has to stop study treatment

• All of this must be documented in the research chart!
Elements of Study Conduction

- Investigator Responsibilities
- Subject Identification/Screening
- Informed Consent Form/Process
- Eligibility Determination & Subject Registration
- Data Collection
- Adverse Events/Serious Adverse Events
- Toxicity Grading/Dose Modifications
- Response Review & Monitoring
Response Review & Monitoring:
RECIST - Response Evaluation Criteria in Solid Tumors

• RECIST - the criteria used to assess impact of a treatment on disease

• Define when cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments
Response Review & Monitoring:
RECIST - Definitions

- Target Lesions
  - Measureable Lesions
  - There are different rules for nodal target lesions and non-nodal target lesions
  - Nodal Lesions are Lymph Nodes:
    - ≥ 15mm short axis for target
  - Non-nodal target lesions must be:
    - ≥ 10 mm long axis when evaluated with CT Scan
    - ≥ 20 mm long axis when evaluated with Chest X-ray
    - ≥ 10 mm long axis with calipers

- Nontarget Lesions/Non-measureable Lesions:
  - Small lesions and all other lesions not qualifying as Target Lesions
  - Truly non-measurable lesions:
    - Bone lesions, Lepteomeningeal disease, Pleural/pericardial effusions and Ascites, Inflammatory breast disease, Lymphangitis cutis/pulmonis, Cystic lesions
Response Review & Monitoring:
RECIST - Definitions

• **Non-Target Lesions**
  • Pathologic lesions too small to be considered target lesions
    Lesions not qualifying as target lesions due to restrictions on the number of target lesions from a single site or total number of target lesions
  • Truly non-measurable lesions
    • Bone lesions
    • Pleural\pericardial effusion and ascites
    • Inflammatory breast disease
    • Lymphangitis cutis/pulmonis
    • Cystic lesions
    • Leptomeningeal disease
Response Review & Monitoring: RECIST - Baseline Reporting

• Purpose: To assess response, it is necessary to estimate the overall tumor burden at baseline in order to compare to subsequent measurements

• Review protocol to ensure baseline measurements are done within timeframe allowed (usually 4 weeks). Try to have them done as close to the start of treatment as possible
Response Review & Monitoring:
RECIST - Follow Up Reporting and Response Criteria

• Follow-up measurements should ALWAYS be made by the same method of evaluation used at Baseline. (i.e. If baseline measurements were done using a CT scan, ALL additional measurements should also be done by using a CT scan)

• Each lesion listed at Baseline must be listed on all follow-up forms in the same order
# Response Review & Monitoring:
## RECIST - Evaluation of Target Lesions

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>Disappearance of all target lesions</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD</td>
</tr>
<tr>
<td><strong>Progressive Disease (PD)</strong></td>
<td>At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions</td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
<td>Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD</td>
</tr>
</tbody>
</table>
Response Review & Monitoring: 
RECIST - Confirmation of Response

• Any Complete Response (CR) or Partial Response (PR) requires a confirmation assessment no less than 4 weeks after the response criteria is met.

• The main goal of confirmation of objective response is to avoid overestimating the response rate observed.
Response Review & Monitoring:
RECIST - References

• www.recist.com

• http://imaging.cancer.gov/clinicaltrials/imaging/

Elements of Study Conduction

- Investigator Responsibilities
- Subject Identification/Screening
- Informed Consent Form/Process
- Eligibility Determination & Subject Registration
- Data Collection
- Adverse Events/Serious Adverse Events
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- Response Review and Reporting
- Data & Safety Monitoring
Data & Safety Monitoring:

Data & Safety Monitoring Committee (DSMC)

- Oversees and monitors all on-going clinical research at the UWCCC and affiliate sites for safety and data quality issues

- Reviews all reports on quality assurance, audits, monitoring and protocol deviations

- Reviews all SAE reporting in real time via the DSMC Chair

- Serves as the DSM body of record for IITs that are internally monitored. These studies incorporate the UWCCC Data and Safety Monitoring Plan (DSMP) into the protocol
Data & Safety Monitoring: Quality Assurance Reviews (QARs)

- QARs are performed on all Investigator-Initiated Trials (IITs) and Cooperative Group protocols after the first two subjects have been accrued to the study or within 6 months after 1st pt is accrued.

- QARs are performed by the QA Coordinator and consist of regulatory, case review and database checks.

- They are designed to identify, early on in the study, any potential problems.

- A QAR report is generated and suggestions for improvements (if applicable) are included in the report.

- QARs constitute a “monitoring” event, which differs from an “auditing” event.
Internal Audits (IAs)

- Internal audits (IAs) are conducted once per year on all Investigator-Initiated Trials conducted at the UWCCC and its affiliates.

- IAs consist of a full review of:
  - Review of a select number of subject cases for:
    - Protocol Compliance
    - Documentation
  - Review of Regulatory documents for:
    - Adherence to regulatory guidelines, reporting of SAEs, approval of protocol amendments, etc.
  - Review of Pharmacy for:
    - Drug accountability

- Audit teams include the Clinical Research Compliance Office (CRCO) Compliance and Monitoring Coordinator, a UWCCC physician and additional audit members (CRAs from the various groups) depending on the number of protocols and subject cases that require review.
Data & Safety Monitoring: Internal Audits (IAs)

• The Compliance and Monitoring Coordinator leads up the audit and conducts the regulatory and pharmacy portions of the audit

• The physician and additional auditors review the selected subject cases

• At the conclusion of an IA, an Exit Interview is conducted with the study PI(s) and the DOWG Program Manager

• An Internal Audit report is generated and sent to the PI. If follow-up is required, a Corrective Action Plan (CAP) is put together by the PI to address any deficiencies that were cited in the audit

• The CAP is sent to the CRCO and the DSMC reviews it at their next meeting and determines if it is acceptable
Data & Safety Monitoring: Response Reviews (RRs)

• The UWCCC Data and Safety Monitoring Plan (DSMP) provides an independent response confirmation as part of its ongoing Quality Assurance program.

• A Response Review is performed on any confirmed radiological partial response (PR) or complete response (CR), as defined in the protocol, on any therapeutic trial that does not have an external review body (i.e. IITs).

• When the investigator believes the best response has been achieved, an independent Response Review is completed by an impartial UWCCC investigator. A system is in place to mitigate if the review does not concur with the reported response.
Data & Safety Monitoring:
Protocol Summary Reports (PSR)

• Protocol Summary Reports are required for all active interventional clinical research studies

• Allows DSMC to monitor the trial in regards to:
  • # of subjects accrued
  • # of SAEs reported
  • # of Protocol Deviations
  • # of Responses

• Frequency of PSR is dependent on the type and phase of the trial:
  • Investigator-Initiated protocols
    • Phase I- quarterly submission to DSMC
    • Phase I/II- Twice yearly submission to DSMC
    • Phase III- Annual submission to DSMC
  • Cooperative Group and Industry protocols
    • Annual submission to DSMC
Quality Assurance/ Monitoring for all Cancer Center Interventional Trials

Investigator Initiated Trials (IIT)

Cooperative Group Trials/ Consortium Trials (CGT/CT)

Industry-Sponsored Trials (IST)

Quality Assurance Review (QAR)
A Quality Assurance Review (QAR) is conducted on all IIT and Cooperative Group trials after the first two subjects are accrued.

Subsequent Monitoring for IIT

Internal Audit (IA)
Annually, each research group will be subject to an IA that audits all open IIT and WON trials for that group.

External Monitoring Visit Reports: All external monitoring reports and DOWG responses are required to be submitted to DSMC Coordinator

Subsequent Monitoring:

Quality Assurance Review (QAR)
All IST are subject to random selection for a QAR for as long as the study is open

All Cancer Center Interventional Trials (IIT, CGT/CT, IST)

Database Monitoring

New Subject Data Check

New Protocol Data Check

Random Database Check

Protocol Summary Reports (PSR)
PSRs are submitted for all studies to the DSMC. Required frequency of a PSR is determined by type of sponsor and phase of study.

Response Review (RR)
Review of all confirmed radiological Partial Response (PR) or Complete Response (CR) on any therapeutic trial regardless of sponsor. Mandatory for studies without external RR process.
## Data Safety & Monitoring:
### DSMS Elements Table

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<th>Sponsor Type</th>
<th>Intervention Trials</th>
<th>Non-Intervention Trials</th>
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<tbody>
<tr>
<td></td>
<td>Therapeutic, Supportive Care, Prevention Protocols</td>
<td>Physical Procedures</td>
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#### DSMS Monitoring Functions

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#### Reports for DSMC Review

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<td>CR Reports</td>
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<td>Protocol Summary Report (PSR)</td>
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<td>Serious Adverse Events (SAEs)</td>
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#### Database Quality Control Measures

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Elements of Study Conduction

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- Response Review and Reporting
- Data & Safety Monitoring
- Protocol Maintenance
Protocol Maintenance:

Regulatory

- **Regulatory Files** - must be updated and maintained throughout the study

- **Protocol Continuing Review** - every year the study must be approved by the IRB and the consent form re-stamped for updated approval

- **Change of Protocol/ Protocol Amendment** - any change to the protocol must go to the IRB as an amendment to the protocol. If the change is administrative (e.g. change of study personnel), the amendment can go through as an expedited change. If the change or amendment meets the major amendment criteria for the PRMC (e.g. change to treatment plan, change to eligibility criteria), it must be submitted first for PRMC approval, then to the IRB

- All reviews, updates, etc. must be entered into OnCore and the most recent study documents must be uploaded
Protocol Maintenance:
Investigational Drug Brochure (IDB)

- An IDB is a document that summarizes pre-clinical and clinical research findings for an investigational agent

- The IDB contains details about the risks and potential benefits of an investigational agent

- The company that has ownership of the investigational agent creates the IDB for that agent

- Periodically, the IDB is revised to include additional information discovered about the investigational agent and is released and sent to all investigators utilizing that agent in a clinical trial
Protocol Maintenance:  
**IDB Revisions**

- When a revised IDB is received, the research staff needs to determine what changes were made.

- Most often, this task is accomplished by comparing the revised IDB to the prior version. Any changes in the revised IDB are then highlighted.

- When all changes in the revised IDB have been identified, the PI reviews the changes and determines if the IDB revisions alter the study’s risk/benefit ratio.

- If the PI feels the risk/benefit ratio of a study has been altered by the new information, he/she will have the research staff revise the consent form and submit to the IRB.
Protocol Maintenance:
IDB - IRB Submission

• The UW-IRB requires that a PI review a revised IDB within 90 days of receiving the document to determine if the risk/benefit ratio has been affected

• If the revised IDB does not alter the risk/benefit ratio, and there are no changes made to the consent form, the IDB can be submitted to the UW-IRB at the time of next continuing review
Protocol Maintenance:
IDB - Other Key Points

• All versions of an IDB should be kept with the regulatory files for the study

• Some studies involve multiple investigational agents, and each of those agents have their own IDB

• An investigational agent may be used in multiple studies. In this case, the PI would need to review the revised IDB in relation to each study and applicable consent forms
Protocol Maintenance: Outside Safety Reports (OSRs)

• An Outside Safety Report (OSR) is a report sent to an investigator by a sponsor that details an SAE occurring at another site involved with the same study or study drug.

• The OSRs get routed to the Clinical Research Services Office after they are reviewed for consideration of safety issues where they are scanned and logged in as being received.

• PIs review all Action Letters and other OSRs that relate to their study.

• If the Action Letter states the AE changes the risk/benefit ratio of the study, he/she will revise the consent form and submit it to the IRB.
Protocol Maintenance:
OSRs - IRB Submission

• If the consent form was revised due to an OSR Action Letter, it needs to be submitted to the IRB promptly, along with the OSR
  • If significant safety issues are involved, the trial may be suspended until IRB review

• If the OSR does not alter the risk/benefit ratio, and no changes are made to the consent form, the OSR information can be submitted to the IRB at the time of next continuing review
Elements of Study Conduction

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- Data & Safety Monitoring
- Protocol Maintenance
- Protocol Completion and Closure
Protocol Completion/Closure

- A study is “completed” when all subjects have gone “off study”, which is after follow-up is completed

- The study can be “closed out” at the IRB when:
  - All data is collected and “locked” for the trial
  - Need to provide the IRB with study closure report that summarizes study closure, subject activity, and AE/SAE information

- If the subjects will still continue to be followed for survival, the study needs to remain open (unless ECOG trial in which case the protocol can be switched to the ELTFU protocol)

- Once the data has been analyzed for the study, it can be submitted for publication

- The study records need to be maintained for a specified amount of time (indicated in protocol)

- Study records can be archived and sent to the State Records Center (SRC)
Protocol Completion and Closure:
UWCCC Study Record Archiving

• Submission of new records to State Records Center for archiving is facilitated by CRSO

• Retrieval of previously stored records is done directly by the Research Group

• Length of time study records need to be maintained is determined by the type of study and sponsor
Teamwork = Success!

Questions?
Contact: swzeldin@uwcarbone.wisc.edu