SOP 3.9

New Mexico Cancer Care Alliance/UNM Cancer Center

External Adverse Event Safety Reports

A. INTRODUCTION AND PURPOSE

The New Mexico Cancer Care Alliance (NMCCA) is a nonprofit entity organized to provide New Mexico cancer patients access to the latest research, technologies and clinical services in prevention, screening, detection, diagnosis/staging, treatment, supportive care, and continued surveillance through collaboration among public and private healthcare providers. The NMCCA participants include community hospitals and private practices located in New Mexico, as well as the University of New Mexico Cancer Center (UNM CC).

Internal adverse events are those adverse events experienced by subjects enrolled in single center or multicenter studies at local sites affiliated with the New Mexico Cancer Care Alliance. In contrast, **external** adverse events are those adverse events experienced by subjects enrolled in studies at sites outside the NMCCA network and are typically safety reports submitted by industry sponsors to site investigators participating in multicenter studies.

The purpose of this document is to outline the policy and specific operational procedures followed by all New Mexico Cancer Care Alliance participant sites, including the UNM Cancer Center, as they relate to the receipt, processing and storage of research-related subject safety reports arising from unaffiliated sites, also known as external adverse events (external AEs) distributed by industry sponsors for NMCCA investigator initiated trials and by industry sponsors of multi-site trials. The reports that are covered by this SOP amay be individual external reports, known as alerts from sources like CIOMS or Medwatch, or are suspected unexpected serious adverse reaction (SUSAR), Action or IND Safety Reports.

As of January 2009, the Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP) issued a guidance clarifying that it is neither useful nor necessary that reports of individual adverse events occurring in subjects enrolled on multicenter trials be distributed routinely to investigators or IRBs at all institutions conducting the research. The NMCCA and its participants, including the UNM Cancer Center have adopted this guidance and will no longer conduct a local review of individual external adverse events forwarded by National Cancer Institute (NCI) Cooperative Group Research Bases, Industry Sponsors or other academic centers sponsoring multi-center trials in which NMCCA sites (including UNM CC) participate.

This procedure and related policy are established to comply in part with:

1) the regulatory requirement n 45 CFR 312.32 (c) (1) (i) which states, "the sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event",

2) the regulatory requirement in 45 CFR 46.103(b)(5) which states, "each IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of any *unanticipated* problems involving risks to subjects or others."

The Food and Drug Administration regulations include the same requirement [21 CFR 56.108(b)(1)]. IRBs must be informed promptly of those adverse events that are 1) serious, 2) unexpected, and 3) related (or "possibly related") to participation in the research,

3) the OHRP January 15, 2007 Guidance Statement: OHRP advises that it is neither useful nor necessary under the HHS regulations in 45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an **unanticipated** problem. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/Data Monitoring Committee, or DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

4) the FDA January 2009 Guidance for Clinical Investigators, Sponsors, and IRBS Adverse Event Reporting to IRBs which states the critical question for studies conducted under part 312 is what adverse events should be considered unanticipated problems that merit reporting to an IRB.

5) the NCI Central Institutional Review Board (CIRB) Memorandum dated April 1, 2010: "Since CTEP-sponsored Phase 3 trials are mandated to have a **study-specific DSMB**, the adult and pediatric CIRBs are changing their current adverse event report review process pertaining to Phase 3 trials to reflect the review recommendations contained in the above cited Guidance" (45 CFR part 46 and 21 CFR 312).

6) the Memorandum of Understanding (MOU) dated 11/1/2011 between UNM Human Research Review Committee, the UNM Cancer Center Clinical Trials Office and the New Mexico Cancer Care Alliance.

B. SCOPE

All clinical trials and investigators conducting non-exempt human research conducted in association with the New Mexico Cancer Care Alliance are subject to this policy. This policy includes external adverse event reports generated by sponsors of trials consistent with the policies of the IRB of record for each study.

C. DEFINITIONS

For the purpose of this policy, the following definitions apply:

Adverse Event (AE): An adverse event is an untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

In general, adverse events are considered **related to participation in the research** if they are at least partially caused by the procedures involved in the research. Adverse events are considered **unrelated to participation in the research** if they are **solely** caused by the subject's disease or condition or by other circumstances unrelated to either the research or to the subject's condition. For examples of adverse events that represent unanticipated problems and need to be reported under the HHS regulations at 45 CFR 46, refer to Appendix D of the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

CTEP: Cancer Therapy Evaluation Program is the department within the NCI Division of Cancer Treatment Diagnosis, responsible for coordinating the largest, publicly funded oncology clinical trials organization in the world

External: Generated from research sites unaffiliated with the New Mexico Cancer Care Alliance

IND: Investigational New Drug a drug not yet approved by the FDA

Possibly Related: an event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.

Related: evidence to suggest a causal relationship between the drug and the adverse event.

Serious Adverse Event: Any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or

SUSAR: *Suspected Unexpected* Serious Adverse Reaction is a serious adverse reaction in a subject given a drug that may or may not be dose related, but are unexpected, as they are not consistent with current information.

Unanticipated: any problem, incident, experience of outcome that is unexpected, related or possibly related AND places subject or others at a greater risk of harm than was previously known or recognized.

Unexpected: an adverse event or a suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk of information described in the general investigational plan or elsewhere in the current application, as amended.

D. POLICY

A. The New Mexico Cancer Care Alliance manages and reports external adverse events once a study has IRB approval and stops managing these events, once the study is closed to the IRB.

B. NMCCA will not review, report or store individual external reports that are distributed as alerts through Medwatch, Cioms, or sponsor specific software.

C. The NMCCA Faculty and Staff will review external IND safety reports (sometimes referred to as SUSAR) that have been provided by the sponsor in writing according to the FDA Code of Federal Regulations (CFR) section 21 CFR 312.32(c) (1) and that specify they are;

1. Unexpected,
2. Related, or possibly related to participation in the research, AND
3. Serious or otherwise suggestive that the research places subjects or others at greater risk of physical or psychological harm than was previously known or recognized.

The IND safety report from the sponsor and reviewed by NMCCA must include:

1. A clear justification as to why the adverse event(s) or series of events is deemed unexpected; AND
2. A clear statement regarding the sponsor's evaluation of the related implications for the ongoing conduct of the related study(ies), generally which results in the issuance of a protocol amendment and/or update to an Investigator's Brochure.

D. NMCCA will retain and report to the IRB of Record, external IND safety reports (SUSAR) that are unanticipated and reportable according to the policies of the IRB of record for the related

clinical study. IND Safety Reports (SUSARs) that are not reportable to the IRB of record will not be retained by NMCCA or its Investigators. If a Sponsor utilizes the Western IRB as the central IRB for their clinical study, the Sponsor is required to report all reportable unexpected serious adverse reaction to WIRB.

E. The NMCCA will continue to rely on Data and Safety Monitoring Board (DSMB) determinations, protocol revisions, and Investigator Brochure (IB) updates provided by the NCI Research Base(s), Industry Sponsors and collaborative academic center trial sponsors. DSMB minutes and recommendations will be submitted to the IRB within 30 working days of receipt from sponsors. Protocol revisions and IB updates will be submitted to the IRB according to requirements of sponsor of trial and the IRB of record.

E. PROCEDURE

Handling external safety reports from Industry Sponsors

- Sponsor
- PI
- Regulatory Coordinator

The following applies to all trials reviewed by the Protocol Review and Monitoring Committee **BEFORE** this SOP's effective date (July 2011):

PI (Co-Investigators) reviews external safety reports received from sponsors to determine if the external adverse event is unanticipated and reportable to the IRB

Report adverse events that are unanticipated, to the IRB of record per their policy. File applicable safety reports in the study regulatory file.

All external adverse events that are NOT unanticipated are considered non-reportable. Non-reportable external adverse events are logged, signed and dated by PI and filed in regulatory binder.

The following applies to all industry sponsored trials reviewed by the Protocol Review and Monitoring Committee **AFTER** this SOP's effective date (July 2011):

External events **that are clearly designated by the study sponsor as:**

1) unexpected, 2) related or possibly related to participation in research **AND** 3) serious, placing the subject or others at a greater risk of physical or psychological harm than was previously known or recognized: and **Sponsor** submits reports with justification regarding unanticipated nature of event directly to local PI.

Review the external event meeting above criteria and if it is considered unanticipated, report to the IRB of record, per the policy of the IRB and retain the external safety event in the regulatory binder.

If the event is not reportable, it will not be retained in the regulatory binder.

Individual External adverse events **that DO NOT meet all of the above criteria or IND safety reports that are received without a report by the sponsor explaining why the events are to be reported, will be destroyed by NMCCA.**

Handling external safety reports from NCI Cooperative Groups, NMCCA Investigator Initiated Trials and other Academic Center-Sponsors

- Sponsor
- PI
- Regulatory Coordinator

The following applies to all NCI Cooperative Group, NMCCA Investigator Initiated and other academic center-sponsored trials reviewed opened **BEFORE** the MOUs effective date (Nov. 1, 2011):

For external adverse events that are unanticipated and meet all of the following conditions:

1) unexpected, 2) related or possibly related to participation in research **AND** 3) serious, placing the subject or others at a greater risk of physical or psychological harm than was previously known or recognized:

PI (Co-Investigators) reviews external safety reports received from NCI Cooperative Group, NMCCA Investigator Initiated and other academic center-sponsored to determine if the external adverse event is reported the local IRB.

File applicable safety reports in the study regulatory file.

All external adverse events NOT meeting all three of the requirements stated in this section are considered non-reportable to the IRB but will be managed according to the policy of the IRB of record.

The following applies to all trials opened (new studies or ongoing) **AFTER** the MOU's effective date (Nov. 1, 2011):

Individual external safety event reports will not be reviewed, logged or maintained, unless the external events **are considered reportable to the IRB of record and clearly designated by the sponsor as being** 1) unexpected, 2) related or possibly related to participation in research **AND** 3) serious, placing the subject or others at a greater risk of physical or psychological harm than was previously known or recognized.

Report adverse events meeting above criteria, as designated by the study sponsor, to the IRB of record per their policy.

File applicable safety reports in the study regulatory file.

Notifications: Satellite and Affiliate Sites

External adverse event reports received in the Clinical Trials Office from external (non-NMCCA or Consortium) clinical sites involved in multi-center trials that involve events which meet the definition of an unanticipated problem (outlined above in this Procedure) and which are considered reportable by the IRB of record will be provided to satellite and affiliate sites which are actively taking part in the related study(ies). Once processed for IRB reporting, documents will be scanned and sent electronically to the lead Research Nurse/Research Coordinator at each participating site. The Research Nurse/Research Coordinator will be responsible for reviewing the event and discussing with his or her site Principal Investigator the potential impact on local research study populations. The responsible regulatory staff member will maintain originals with copies of email distributions in the official study regulatory binder.

E. RELATED REFERENCES

1) DHHS Regulations: 45 CFR 46.103(b)(5); 45 CFR 46.113

2) FDA Regulations: 21 CFR 56.108(b)(1); 21 CFR 56.113; 21 CFR 312.32(c)

3) Office for Human Research Protections (OHRP) Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007.

4) Food and Drug Administration Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs Improving Human Subject Protection, January 2009.

5) 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice

6) UNM Health Sciences Center Human Research Protections Manual, v. 2008

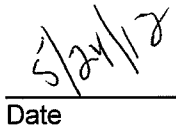
7) http://www.wirb.com/content/inv_adverse_events.aspx, Western IRB requirements for reporting unanticipated problems

8) http://www.ncicirb.org/CIRB_AE_Review_Process_Memo_040110.pdf NCI Central IRB Policy Update: External AE Review Process, April 2010.

9) CTO/NMCCA Process 2011-EAE-01: External Safety Report Memorandum of Understanding (MOU) Agreement (Nov 2011)

10) Human Research Protections Manual for the UNM HSC HRRC (November 2010)

NMCCA Medical Director



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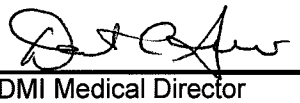
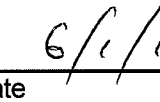


CPDMI Medical Director



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