University of New Mexico Comprehensive Cancer Center / New Mexico Cancer Care Alliance

STANDARD OPERATING PROCEDURE

Clinical Research Office

Title: NEW MEXICO CANCER CARE ALLIANCE/UNM CANCER CENTER EXTERNAL ADVERSE EVENT SAFETY REPORTS

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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).

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 may 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.

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.

APPLICABLE REGULATIONS AND GUIDELINES

N/A

REFERENCES TO OTHER APPLICABLE SOPs

N/A

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 at NMCCA sites.

B. Consistent with the updated 2015 FDA guidance on IND safety reporting, NMCCA only accepts IND safety reports from sponsors that the Sponsor has determined meet the requirements of reporting to the FDA, by the Sponsor.

As defined in the 2015 FDA guidance, the FDA now requires sponsors to file IND safety reports for suspected adverse reactions that are both serious and unexpected. The guidance states that there must be a "reasonable possibility" the drug caused the adverse event – that is, there must be evidence to suggest a causal relationship.

The FDA provides three examples of when such a "reasonable possibility" of causality may be drawn, requiring an IND safety report:

- When the event is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens - Johnson syndrome)

- When the event is not commonly associated with drug exposure, but is uncommon in the population exposed to the investigational drug (e.g., tendon rupture)
- When an aggregate analysis of specific events indicates the events occur more frequently in the drug treatment group than in controls

In accordance with ICH 5.16.2, the sponsor should "promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial". Additionally, in accordance with ICH 8.3.18, the NMCCA agrees to acknowledge, file, and report as applicable the IND safety reports that meet FDA guidelines of reportable and meet the definition of ICH 5.16.2.

The NMCCA requires that Sponsors provide a memo with the IND safety report stating that the Sponsor has assessed the safety report and they meet the definition of reportable to the FDA. For those IND safety reports that are determined reportable, the NMCCA agrees to document and maintain a record of the PI's review, as well as the printed IND safety report. A memo stating that the PI has reviewed "IND safety assessment #s X that were received on (insert date) and has no, or the following comments" is created and signed by the PI/sub-I. This memo is maintained with the corresponding IND reports.

Because it is the sponsor's responsibility to determine what meets the definition of reportable, NMCCA will not accept any IND safety reports that have not been determined by the sponsor to meet the definition of reportable, because NMCCA does not have any of the necessary information to be able to make an informed decision about reports, of the aggregate analysis being performed, of the safety monitoring committee assessments, or the individual subject's medical history or treatment course. In the absence of this information, the NMCCA and investigator believe they are being put in the position of making sponsor level assessments for subjects for which there is no medical or scientific knowledge. The investigator can only assess the seriousness and causality of events for his/her own subjects using her/her personal knowledge of the subject's history, treatment and disease course.

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. The NMCCA will only report safety information based on the Western IRB's requirement listed below.

Information not listed below does not require prompt reporting to WIRB:

1. New or increased risk
2. Protocol deviation that harmed a subject or placed subject at risk of harm
3. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
4. Audit, inspection, or inquiry by a federal agency
5. Written reports of federal agencies (e.g., FDA Form 483)
6. Allegation of Noncompliance or Finding of Noncompliance

7. Breach of confidentiality
8. Unresolved subject complaint
9. Suspension or premature termination by the sponsor, investigator, or institution
10. Incarceration of a subject in a research study not approved to involve prisoners
11. Adverse events or IND safety reports that require a change to the protocol or consent
12. State medical board actions
13. Unanticipated adverse device effect
14. Information where the sponsor requires prompt reporting to the IRB

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.

PROCEDURES

Handling external safety reports from Industry Sponsors

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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.

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) ICH Guidelines: ICH 5.16.2, ICH 8.3.18

4) 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.

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

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

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

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

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

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

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