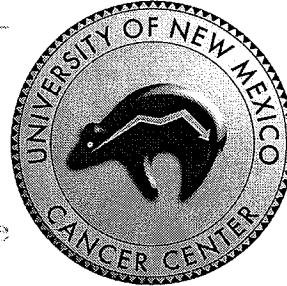
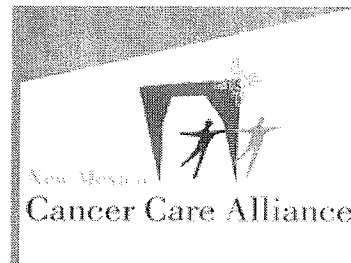


SOP 3.9

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 that are at Centers or practices 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.

As of January 2009, the Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP) issued guidances 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 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. 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

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

1) 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,

2) 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.

3) 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).

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 or unfavorable medical occurrence in a human research subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, *temporally* associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

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.

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.

CTEP: Cancer Therapy Evaluation Program (National Cancer Institute)

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

IND: Investigational New Drug

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

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

any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above

SUSAR: *Suspected Unexpected Serious Adverse Reaction* report

Unanticipated: not consistent with either the risks described in the study-related documents including a protocol, informed consent document, or Investigator's Brochure OR with the natural progression of the subject's underlying disease or condition.

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. Events that meet all three of the following criteria **as evaluated by the study sponsor** will be reported to the NMCCA study IRB of record in accordance with IRB-specific guidelines and documentation requirements:

- 1) unanticipated;
- 2) Related or possibly related to participation in the research;
- 3) Serious, i.e. that places the subject or others at a greater risk of physical or psychological harm than was previously known or recognized.

C. External events that meet all of three criteria must be communicated by the research sponsor directly to the local NMCCA Principal Investigator.

The report must include the following **from the study sponsor**:

- 1) A clear explanation of why the adverse event or series of adverse events has been determined to be an *unanticipated* problem;
- 2) The specific implications for the conduct of the study in our local population. For example: does the event warrant a temporary or permanent closure to further accrual? Does the

sponsor intend to modify the study eligibility as a result of the event(s)? Will the informed consent document and/or Investigator Brochure require amendment?

D. In accordance with the updated SOP 3.9, dated July 2011, events that do not meet the above criteria are considered **non-reportable** external events. These should not be reported to the NMCCA investigator(s) as individual reports. Such reports will not be reviewed, retained or otherwise managed by the New Mexico Cancer Care Alliance or its participants, including UNM Cancer Center investigators and staff.

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):
- For external events that meet all of the following conditions:
- 1) unanticipated,
 - 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 sponsors to determine if the external adverse event is medically significant to the local study population, requiring reporting to the IRB
- 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.
- All external adverse events NOT meeting all three of the requirements stated in this section are considered non-reportable. Non-medically significant 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):

For external events **that meet all of the following conditions are considered reportable, as designated by the study sponsor:**

- 1) unanticipated,
- 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:

Sponsor submits reports with justification regarding unanticipated nature of event directly to local PI;

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.

All external adverse events NOT meeting all three of the requirements stated in this section, are considered non-reportable. These are not to be reviewed, retained or otherwise managed by the NM Cancer Care Alliance investigators or staff.

External events **that DO NOT meet all of the conditions or 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 by the Protocol Review and Monitoring Committee **BEFORE** this SOP's effective date (Nov. 1, 2011):

For external events that meet all of the following conditions:

1) unanticipated,

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 medically significant to the local study population, requiring reporting to the IRB

Report adverse events meeting above criteria, as designated by the Investigator, to the IRB of record per their policy. 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. Non-medically significant external adverse events are logged, signed and dated by PI and filed in regulatory binder.

The following applies to all trials reviewed by the Protocol Review and Monitoring Committee **AFTER** this SOP's effective date (Nov. 1, 2011):

For external events **that meet all of the following conditions are considered reportable, as designated by the sponsor:**

1) unanticipated,

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:

Sponsor submits reports with justification regarding unanticipated nature of event directly to local PI;

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.

All external adverse events NOT meeting all three of the requirements stated in this section, are considered non-reportable. These are not to be reviewed, retained or otherwise managed by the NM Cancer Care Alliance investigators or staff.

External events **that DO NOT meet all of the conditions or are received without a report by the sponsor explaining why the events are to be reported, will be destroyed by NMCCA.**

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) 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice
- 5) UNM Health Sciences Center Human Research Protections Manual, v. 2008
- 6) http://www.wirb.com/content/inv_adverse_events.aspx, Western IRB requirements for reporting unanticipated problems
- 7) http://www.ncicirb.org/CIRB_AE_Review_Process_Memo_040110.pdf NCI Central IRB Policy Update: External AE Review Process, April 2010.
- 8) CTO/NMCCA Process 2011-EAE-01: External Safety Report Management Agreement (Nov 2011)
- 9) Human Research Protections Manual for the UNM HSC HRRC (November 2010)



NMCCA Medical Director

11/16/11

Date



CPDMI Medical Director

11/14/11

Date