# Section 3: Special Issues

# 3.1 Assessing the Need for Increased Monitoring, Interim Continuing Review, and Verification from Sources Other than the PI

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for determining the need for: 1) IRB review more often than annually, 2) increased monitoring, and 3) verification from sources other than the PI that no material changes have occurred since previous IRB review.

## 2.0 Policy

It is the policy of the Organization that that all non-exempt research will be assessed at both initial and continuing review in accordance with the requirements set forth by HHS regulations at 45 CFR 46.103(b)(4), FDA regulations at 21 CFR 56.108(a)(2), and all applicable state and local laws.

## 3.0 Increased Monitoring and/or Interim Continuing Review

- **3.1.** At the time of initial review, continuing review, or any other event, the IRB may decide that a research protocol requires increased monitoring and/or interim continuing review. Types of research which might require such actions include, but are not limited to:
  - **3.1.1.** Studies that utilize drugs or treatments associated with a higher than typical risk of toxicity.
  - **3.1.2.** Studies where there is an expectation of high morbidity and mortality due to the underlying medical condition of the subjects.
  - **3.1.3.** Studies whose design includes one or more group of subjects who will receive less than standard care (for example, use of placebo where there is an active alternative treatment, or withholding standard treatments during some point in the study), or where there is a significant risk intervention that is performed solely for research purposes.
  - **3.1.4.** Studies where the FPBCC Scientific Review Committee (SRC), or other equivalent scientific review body, has indicated the need for interim review or additional monitoring.
  - **3.1.5.** Any other situation where the IRB believes that increased monitoring or interim continuing review will meaningfully protect the rights and welfare of human subjects of the research.
- **3.2.** When the IRB determines the need for increased monitoring this may be accomplished by either: 1) submission of interim reports by the PI, or 2) auditing of PI records by the IRB Administrator and/or an IRB member(s). The PI will be notified of these requirements in writing.
- **3.3.** If the IRB determines the need for more frequent continuing review the PI will be notified in writing and the IRB approval period will be set accordingly.

## 4.0 Verification from Sources Other than the Investigator

- **4.1.** At the time of initial review, continuing review, or any other event, the IRB may decide that a research protocol requires verification from sources other than the PI that no material changes have occurred since the previous IRB review. Research that falls in any of the following categories may warrant consideration of verification from sources other than the PI:
  - **4.1.1.** Research performed by investigators with a history of significant noncompliance, recurrent delays in submitting amendments, high number of IRB approval expirations, or failure to respond to IRB review letters or other correspondence in a timely manner.
  - **4.1.2.** Research conducted at external sites where the UNMC IRB is the IRB of record.

- **4.2.** When the IRB determines that verification from sources other than the PI is necessary the designated IRB Administrator and/or IRB member(s) will perform the necessary verification by conducting an audit.

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# 3.2 Data and Safety Monitoring

## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for data and safety monitoring for non-exempt research.

## 2.0 Policy

It is the policy of the Organization that all non-exempt research must have an appropriate plan for data and safety monitoring in consideration of the nature and risk level of the research. The Data and Safety Monitoring Plan (DSMP) may or may not include a formal Data and Safety Monitoring Board (DSMB).

## 3.0 Data and Safety Monitoring Plan (DSMP)

- 3.1. The DSMP must be developed to fit the design and risk profile of the research. It should include, as appropriate, elements such as:
  - 3.1.1. The specific data that will be reviewed
  - 3.1.2. The frequency and duration of review (when monitoring wil start and when it will end).
  - 3.1.3. The identities of the persons or groups conducting the review
  - 3.1.4. The conditions under which specific subjects should be withdrawn
  - 3.1.5. As appropriate based on the design and risk profile of the research, the conditions under which the study will be halted (that is, study stopping rules based on efficacy, toxicity and futility)
- 3.2. The DSMP may include monitoring by the investigator and/or study staff, by faculty advisor, by a sponsor appointed medical monitor or CRO, by an independent monitor or monitoring group (not directly involved with the design and conduct of the study), or by a formal DSMB.

## 4.0 Data Safety Monitoring Board (DSMB)

- 4.1. Under certain circumstances, the IRB or the investigator may decide that the DSMP should include a formal DSMB.
  - 4.1.1. In general a formal DSMB is required for:
    - 4.1.1.1. Phase III clinical trials, with the exception of low-risk behavioral and nutritional studies (such as those where subjects are expected to experience only minor side effects, and interim analyses are not crucial for the protection of subjects).
    - 4.1.1.2. Multicenter randomized phase II clinical trials, with the exception of low-risk behavioral and nutritional studies.
    - 4.1.1.3. High risk phase II clinical trials (such as those involving interventions associated with risk of serious morbidity or death, studies involving diseases associated with high mortality or morbidity, and research involving highly experimental therapies).
  - 4.1.2. In consideration of other trials, a formal DSMB should be considered for the following types of research:
    - 4.1.2.1. Research involving a large study population, or multiple study sites.
    - 4.1.2.2. Research intended to provide definitive information about effectiveness and/or safety of a medical intervention.
    - 4.1.2.3. Research which involves an intervention with the potential to induce unacceptable toxicity.
    - 4.1.2.4. Research which evaluates mortality or another major endpoint, such that

inferiority of one treatment arm has safety as well as effectiveness implications.
    - 4.1.2.5. Research for which it would ethically be important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed.
    - 4.1.2.6. Research involving a particularly vulnerable population, for whom closer monitoring will provide additional meaningful protection.

## 5.0 Review of the DSMP by the IRB

- 5.1. The IRB will consider the adequacy of the DSMP based on the conditions described in section 3.1 above.
- 5.2. For studies that do not have a data monitoring committee the IRB will carefully review the data and safety monitoring plan and determine whether a data monitoring committee would provide meaningful additional protection for subjects.
- 5.3. If the research design or risk profile warrants a formal DSMB the investigator must provide the DSMB charter, or describe (1) the composition of the DSMB membership, (2) the frequency of DSMB meetings and reports. It is expected that most studies which require a formal DSMB will also have formal stopping rules for efficacy and toxicity.
- 5.4. The IRB will evaluate the DSMP in order to ensure that it represents adequate provision for monitoring the data collected to ensure the safety of subjects.

## 6.0 Review of DSMB Reports by the IRB

- 6.1. It is the responsibility of the investigator to obtain copies of, and review, DSMB reports, as they are produced, at the frequency described in the approved IRB application.
- 6.2. The PI is responsible for submitting copies of all DSMB reports to the IRB at the time of continuing review (or interim reporting period as mandated by the IRB).
- 6.3. If the DSMB report finds serious risks to the welfare of subjects, or recommends substantive changes to the protocol (including but not limited to halting of the protocol or accrual) or substantive changes to the informed consent document, then the investigator must submit the report promptly to the IRB. It is expected that such DSMB reports will be followed promptly by a Request for Change in protocol.
- 6.4. If the DSMB finds serious risks to the welfare of subjects, the IRB will take action in accordance with HRPP policy 8.6 (Study Hold, Suspension, and Termination).
- 6.5. If the DSMB report is due but has not been submitted at the time of continuing review (or interim reporting period as mandated by the IRB), the IRB may table the Continuing Review, or may suspend the study in accordance with HRPP policy 8.6 (Study Hold, Suspension, and Termination.

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Revised 12/22/2022 – Clarified expected contents of DSMP; other revisions to eliminate duplicate text and for clarity. {Approved Chris Kratochvil (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

Board notified - 12/29/2022

# 3.3 Privacy Interests and Confidentiality of Research Data

## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for 1) protection of privacy interests of research subjects, and 2) maintenance of confidentiality of data. For the purposes of this policy "subjects" and "participants" are synonymous, and includes those persons participating in a data registry or biobank.

## 2.0 Policy

It is the policy of the Organization that:

- 2.1. The privacy interests of participants, and the confidentiality of research data will be protected in consideration of the risk to subjects and the nature of the research performed.
- 2.2. Protected Health Information (PHI) will be protected in accordance with HRPP policy 3.4 (Use of Protected Health Information in Research).

## 3.0 Definitions

- 3.1. Privacy is defined as having control over the extent, timing, and circumstances of sharing oneself (i.e. a participant's interest in controlling access to themselves).
- 3.2. Private Information is defined as information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- 3.3. Protected Health Information (PHI) is defined as individually identifiable health information, whether oral or recorded in any medium, that:
  (1) is created or received by the Organization; and
  (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.
- 3.4. Confidentiality refers to protecting data in order to ensure that it is not improperly divulged.
- 3.5. Identifiable sensitive information is defined as information that is about an individual and that is gathered or used during the course of research where the following may occur
  (1) through which an individual is identified; or
  (2) for which there is at least a very small risk, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identify of an individual (NIH CoC policy and 42 U.S. Code §241(d)).

*Note that the regulations focus on the identifiability of the information, and not on the sensitivity of the information.*

# 4.0 Protection of Privacy

- 4.1. The IRB will review all applications to determine whether there are adequate provisions to protect the privacy interests of the participants. The greater the risk to privacy, the greater the need to have more stringent protections in place. The IRB will consider the nature and degree of risk to the privacy interests of the participants and the participants' expectations of privacy. The board will make the following determinations as appropriate:
  - 4.1.1. The PI and other research personnel have ethical access to the participant's private, identifiable information in accordance with HRPP policy 3.12 (Ethical Access).
  - 4.1.2. The methods used to identify and contact potential participants minimize the risk to privacy.
  - 4.1.3. The location where informed consent will be obtained is conducive to the privacy interests of participants.
  - 4.1.4. Persons present during the informed consent process or during research activities will be limited as much as is possible to those listed on the IRB application or involved in the clinical care of the participant, or with the consent of the participant.
  - 4.1.5. The research activities are performed in as private a place as possible.

# 5.0. Protection of Confidentiality

- 5.1. The IRB will review all applications to determine whether there are adequate provisions to protect the confidentiality of data. The greater the risk to the subject associated with a breach of confidentiality, the more stringent must be the protections in place. The IRB will consider the participants' expectations for confidentiality and the nature and degree of risk associated with loss of confidentiality. The board will make the following determinations as appropriate:
  - 5.1.1. The physical and/or electronic safeguards and security measures for the entry, storage, and transfer of data are adequate in consideration of the nature of the data, the risk to the subject associated with a breach of confidentiality and the physical medium on which the data is stored. PHI must be stored in a manner that is compliant with the HIPAA Privacy Rule, and other regulations and laws as applicable.
  - 5.1.2. There is adequate justification for sharing identifiable private information, and PHI is shared in a manner that is compliant with the HIPAA Privacy Rule, and other regulations and laws as applicable.
  - 5.1.3. The minimum amount of identifiable private information necessary to complete the study will be maintained, and access to identifiable private information will be restricted to the minimum number of persons with a legitimate need.
  - 5.1.4. Identifiable private information will be appropriately and safely destroyed when it is no longer needed, as allowed under HRPP policy 1.17 (Retention of Research Records).
- 5.2. Certificate of Confidentiality
  - 5.2.1. Research is automatically covered by an NIH Certificate of Confidentiality whenever the study is funded in whole or in part by the NIH and involves identifiable, sensitive information. Such research includes, but is not limited to:
    - 5.2.1.1. Biomedical, behavioral, clinical or other research, including exempt research, except where the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.

- 5.2.1.2. The collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.
- 5.2.1.3. The generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified, or the identity of the human subjects can readily be ascertained.
- 5.2.1.4. Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.
- 5.2.1.3. Researchers may also apply to the NIH for a Certificate of Confidentiality for research not funded by NIH. Generally, NIH will consider these requests for research on a topic that is within the NIH mission or HHS health-related research mission, and for research information that is collected, used, or stored in the US.
- 5.2.1.4. When research is covered by an NIH Certificate of Confidentiality, researchers:
  - 5.2.1.4.1. May not disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
  - 5.2.1.4.2. May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
  - 5.2.1.4.3. May disclose information if:
    - 5.2.1.4.3.1. required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding.
    - 5.2.1.4.3.2. necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
    - 5.2.1.4.3.3. made with the consent of the individual to whom the information, document, or biospecimen pertains; or
    - 5.2.1.4.3.4. made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.
- 5.2.1.5. When research is covered by an NIH Certificate of Confidentiality, researchers must inform participants (for example, in the consent document) of the protections and limitations of certificates of confidentiality.
- 5.2.1.6. Researchers conducting NIH-supported research covered by a Certificate of Confidentiality must ensure that if identifiable, sensitive information is provided to other researchers or organizations, regardless of whether or not that research is federally funded, the other researcher or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.
- 5.2.1.7. All identifiable, sensitive information collected or used for research under an NIH Certificate of Confidentiality are protected by the certificate in perpetuity. However, information collected during a lapse in NIH funding, or after the funding ends, would not be protected by the certificate. Therefore, the consent form for subsequent subjects should be amended to remove any guarantees of protection for these new subjects.

- 5.2.2. Investigators whose research is funded by the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), Indian Health Service (IHS), and Substance Abuse and Mental Health Services Administration (SAMHSA) may also have access to Certificates of Confidentiality thru those agencies.

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Board Notified: 11/29/2022

Revised 1/21/2024 – added definition of “identifiable sensitive information” (section 3.5); elaborated on types of research which are automatically issued a CoC by NIH (section 5.2) {Approved Russell McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

# 3.4 Use of Protected Health Information in Research

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for ensuring the appropriate protections for use of Protected Health Information (PHI) in research.

## 2.0 Policy

- **2.1.** It is the policy of the Organization that investigator access to records containing PHI will comply with: 1) HHS regulations at 45 CFR 46.111(a)(7) and 45 CFR 164.512(i) (HIPAA Privacy and Security Act); 2) 21 CFR 11 (as applicable), 3) UNMC policies #6045, 6057, 6059, 6061, 6071; and 4) UNMC Board of Regents Executive Memorandum No. 27 (HIPAA Compliance Policy).
- **2.2.** It is the policy of the Organization that all patients have a right to privacy which precludes the use of their records containing any PHI by an individual who does not have permitted access as defined in HRPP policy 3.12 (Ethical Access).
- **2.3.** It is the policy of the Organization that records containing PHI, in any form, are the property of the Organization, and that the PHI contained in the record is the property of the individual who is the subject of the record.
- **2.4.** It is the policy of the Organization that, when using or disclosing PHI or when requesting PHI from another covered entity, the investigator must make reasonable efforts to limit protected health information to the minimum necessary to accomplish the research.
- **2.5.** It is the policy of the Organization that a compound authorization process for research will be used where the HIPAA authorization is merged within the research ICF.

## 3.0 Definitions

- **3.1.** ***Protected Health Information (PHI)*** is individually identifiable health information, whether oral or recorded in any medium, that:
  - **3.1.1.** Is created or received by the Organization; and
  - **3.1.2.** Relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual (45 CFR 160.103).
- **3.2.** ***HIPAA Identifiers*** are the characteristics of health information that make such information about the individual (or of relatives, employers, or household members of the individual) identifiable. Per the HIPAA Privacy Rule (45 CFR 164.51(b)(2)(i)), identifiers include the following:
  - **3.2.1.** Names
  - **3.2.2.** All geographic subdivisions smaller than a state, including street address, city county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if, according to the current publicly available data from the Bureau of the Census:
    - **3.2.2.1.** The geographic unit formed by combing all zip codes with the same three initial digits contains more than 20,000 people, and
    - **3.2.2.2.** The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people are changed to 000.
  - **3.2.3.** All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;

- **3.2.4.** Telephone numbers
- **3.2.5.** Fax numbers
- **3.2.6.** Electronic mail addresses
- **3.2.7.** Social security numbers
- **3.2.8.** Medical record numbers
- **3.2.9.** Health plan beneficiary numbers
- **3.2.10.** Account numbers
- **3.2.11.** Certificate/license numbers
- **3.2.12.** Vehicle identifiers and serious numbers, including license plate numbers
- **3.2.13.** Device identifiers and serial numbers
- **3.2.14.** Web Universal Resource Locators (URLs)
- **3.2.15.** Internet Protocol (IP) address numbers
- **3.2.16.** Biometric identifiers, including finger and voice prints
- **3.2.17.** Full face photographic images and any comparable images
- **3.2.18.** Any other unique identifying number, characteristic, or code

- **3.3.** Limited Data Set means health information that excludes the direct HIPAA identifiers listed in section 3.2 above, except that it may include:
  - **3.3.1.** City; state; ZIP Code; and
  - **3.3.2.** Elements of date; and
  - **3.3.3.** Other numbers, characteristics, or codes not listed as direct identifiers
- **3.4.** ***Honest Broker*** (as defined in UNMC Policy 6074 is a neutral intermediary (person or system), who is a workforce member and is certified to collect specified health information from the tissue or data bank, remove all patient identifiers, and provide the de-identified health information or tissue to research investigators, clinicians, or other healthcare workforce members, in such a manner that it would not be reasonably possible for any individual to identify the patients directly or indirectly.

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## 4.0 Use or Disclosure of PHI for Research

The Privacy Rule permits the Organization to use or disclose PHI for research only under certain circumstances and conditions as described below:

- **4.1.** The subject of the PHI has granted specific written authorization, in accordance with 45 CFR 164.508(c).
  - **4.1.1.** The Organization utilizes a compound authorization process for research in which the HIPAA authorization is merged within the research ICF
  - **4.1.2.** The HIPAA Authorization must include the following Core Elements per 45 CFR 164.508(c)(1):
    - **4.1.2.1.** Description of PHI to be used or disclosed (identifying the information in a specific and meaningful manner).
    - **4.1.2.2.** The name(s) or other specific identification of person(s) or class of persons authorized to make the requested use or disclosure.
    - **4.1.2.3.** The name(s) or other specific identification of the person(s) or class of persons who may use the PHI or to whom the covered entity may make the requested disclosure.
    - **4.1.2.4.** Description of each purpose of the requested use or disclosure. This section must “adequately describe such purposes such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for such future research.” (78 FR 5612, 2013)
    - **4.1.2.5.** Authorization expiration date or event (for example, "end of the research study" or "none")
    - **4.1.2.6.** Signature of the individual and date. If the Authorization is signed by an individual's personal representative, a description of the representative's authority to act for the individual.
  - **4.1.3.** The HIPAA Authorization must include the following Required Statements, per 45 CFR 164.508(c)(2):
    - **4.1.3.1.** The individual's right to revoke his/her Authorization in writing and either (1) the exceptions to the right to revoke and a description of how the individual may

revoke Authorization.
    - **4.1.3.2.** Notice of the covered entity's ability or inability to condition treatment, payment, enrollment, or eligibility for benefits on the Authorization, including research-related treatment, and, if applicable, consequences of refusing to sign the Authorization.
    - **4.1.3.3.** The potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This statement does not require an analysis of risk for re-disclosure but may be a general statement that the Privacy Rule may no longer protect health information.
      *Note: The templates for the ICFs are designed to meet all of the regulatory requirements required under the HIPAA regulations.*
  - **4.1.4.** A research subject may revoke his/her Authorization at any time. However, the investigator may continue to use and disclose PHI that was obtained before the individual revoked Authorization. This would permit the investigator to continue using or disclosing the PHI as necessary to maintain the integrity of the research, as, for example, to account for a subject's withdrawal from the research study, to conduct investigations of scientific misconduct, or to report adverse events.
- **4.2.** The PHI will be used for reviews preparatory to research per 164.512(i)(1)(ii)
  - **4.2.1.** Activities "preparatory to research" include, but are not limited to, (1) preparing a research protocol, (2) assisting in the development of a research hypothesis, or (3) aiding in research recruitment, such as identifying prospective research participants who would meet the eligibility criteria for enrollment into a research study.
  - **4.2.2.** The investigator must have ethical access to the PHI in accordance with HRPP policy 3.12 (Ethical Access).
  - **4.2.3.** PHI obtained and recorded may not be removed from the Organization during the course of the review.
  - **4.2.4.** PHI obtained and recorded may not be used for research purposes other than those described above without IRB approval
  - **4.2.5.** Activities “preparatory to research” may still constitute “research” under 45 CFR 46, and therefore, may require informed consent under 45 CFR 46.116, even though HIPAA requirements are met.
- **4.3.** The IRB or Privacy Board has granted a waiver of Authorization per 164.512(i) and HRPP policy 5.2 (Waiver or Alteration of Informed Consent and HIPAA Authorization).
- **4.4.** The PHI has been de-identified per 45 CFR 164.514(b) or (c) (in which case, the health information is no longer PHI)
  - **4.4.1.** PHI is de-identified (and therefore becomes health information and no longer PHI) if either of the following applies:
    - **4.4.1.1.** A person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable (a) applying such principles and methods, determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information; and (b) documents the methods and results of the analysis that justify such determination; OR
    - **4.4.1.2.** The identifiers of the individual or of relatives, employers, or household members of the individual listed in section 3.2 (HIPAA Identifiers) are removed, and the Organization does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information 45 CFR 154.512(b)(2)(ii).
  - **4.4.2.** De-identification is performed by the designated “honest broker” in the Office of the Vice-Chancellor for Research, following the procedure described in UNMC Policy 6074.
- **4.5.** The PHI is released in the form of a Limited Data Set (as defined in section 3.3 above), with a data use agreement between the researcher and the Organization per 45 CFR 164.514(e)
  - **4.5.1.** The Data Use Agreement (DUA): 1) establishes the permitted uses and disclosures of the information by the recipient of the Limited Data Set, and 2) establishes who is permitted use or receive the data set and (3) specifies that the recipient of the LDS will:
    - **4.5.1.1.** Not use or further disclose the information other than as permitted by the DUA/DTA or as otherwise required by law.

        - **4.5.1.2.** Use appropriate safeguards to prevent use or disclosure of the information other than as provided for by the DUA.
        - **4.5.1.3.** Report to the Organization (the ORA and the Privacy Office) any use or disclosure of the information not provided for by its DUA of which it becomes aware.
        - **4.5.1.4.** Ensure that any agents, including a subcontractor, to whom it provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to such information.
        - **4.5.1.5.** Not attempt to identify or contact the individuals.
    - **4.5.2.** The DUA will be negotiated through Sponsored Programs Administration.
    - **4.5.3.** The investigator must have ethical access to the PHI in accordance with HRPP policy 3.12 (Ethical Access).
    - **4.5.4.** The LDS will be prepared by the designated "honest broker" in the Office of the Vice-Chancellor for Research, following the procedure described in UNMC Policy 6074.

## 5.0 Procedures

- **5.1.** Research Involving the Use of PHI
    - **5.1.1.** The Investigator must submit the IRB application that is appropriate for the proposed research in accordance with HRPP policy 2.1 (Submission of Items for Review by the IRB).
    - **5.1.2.** Applications requiring full IRB review will be reviewed in accordance with HRPP policy 2.2 (Full IRB Review).
    - **5.1.3.** Applications that are eligible for review by the expedited method will be reviewed in accordance with HRPP policy 2.3 (Expedited Review of Research).
    - **5.1.4.** Applications which are eligible for exemption under 45 CFR 46.101(b) (or rev 45 CFR 46.104(d)) or 21 CFR 56.104(d) will be processed and reviewed in accordance with HRPP policy 2.6 (Exempt Research).
    - **5.1.5.** In all cases, the minimum amount of PHI should be recorded, and, whenever possible, data should be recorded without PHI.
    - **5.1.6.** Individuals who do not have ethical access to records containing PHI (as defined in HRPP policy 3.12; Ethical Access) must obtain data from the designated "honest broker" as described in section 4.4 above, or which has only a one-way code (for which the custodian of the records has the link and the code is not any part of the 18 HIPAA identifiers).
    - **5.1.7.** If the PHI will be sent to an external entity, a Data Use Agreement or sponsored agreement must be finalized by Sponsored Programs Administration prior to final IRB approval
- **5.2.** Research Utilizing Decedent PHI
    - **5.2.1.** Research involving decedents does not constitute human subject research under 45 CFR 46. However, HIPAA applies to PHI of individuals deceased for 50 years or less; therefore, the IRB, in its capacity as HIPAA Privacy Board, must review the use of such PHI.
    - **5.2.2.** To approve the use of PHI, the IRB, in its capacity as HIPAA Privacy Board, must obtain from the researcher who is seeking access to decedents' PHI:
        - **5.2.2.1.** Oral or written assurance that the use or disclosure sought is solely for research on the PHI of decedents.
        - **5.2.2.2.** Oral or written assurance that use or disclosure of the PHI is necessary for the purposes of the research.
        - **5.2.2.3.** Documentation, at the request of the Organization, of the death of the individuals whose PHI is sought.
    - **5.2.3.** An investigator conducting such research is not required to obtain Authorizations from the personal representative or next of kin under the Privacy Rule; however, permission may be required by State Law, and is certainly respectful of the survivors. Investigators should contact the UNMC Office of the General Counsel.
    - **5.2.4.** The HIPAA Privacy Rule does not apply to identifiable health information on individuals who have been deceased for more than 50 years (45 CFR 164.512(i)(1)(iii)). Therefore, research involving health information from such individuals does not require review or approval of the Privacy Board.

DOCUMENT HISTORY:

Written: 1/28/2016 (Approved: 1/28/2016) - original author not recorded

Revised: 4/9/2018 - revision not documented

# 3.5 Subject Recruitment Through Advertisements

## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for recruitment of subjects through advertisements. For the purpose of this policy, "advertisements" refer to printed advertisements (including bulletins, newsletters, posters, fliers, and magazine or newspaper ads); radio and television advertisements; and electronic advertisements (including social media or other on-line venue).

*Note: Invitations to participate directed to specific persons are covered by HRPP policy 3.6 (Subject Recruitment Through Direct Invitation).*

## 2.0 Policy

It is the policy of the Organization that

- **2.1.** All advertisements related to research for which the UNMC IRB is the IRB of record, must be reviewed and approved by the IRB before the material can be used to recruit potential subjects.
- **2.2.** All advertisements related to research for which the Organization is relying on another IRB as the IRB of record, must adhere to this policy; however, the ORA will not routinely review such advertising unless requested to do so by the investigator or the reviewing IRB.
- **2.3.** Advertising must be clear, promote equitable enrollment and not represent undue influence or coercion.
- **2.4.** For the purpose of this policy, references to information provided to, or decisions made by, potential subjects also means information provided to, or decisions made by, parents, guardians or legally authorized representatives (LARs) as appropriate.

## 3.0 General Requirements and Prohibitions

- **3.1.** Advertisements should be limited to information a potential subject may need to determine if he/she is interested and eligible to participate in a study.
- **3.2.** Advertisements may not include any of the following:
  - **3.2.1.** Statements implying a certainty of a favorable outcome or other benefits beyond those described in the consent document and the protocol.
  - **3.2.2.** Claims, either explicit or implicit, that the research procedures (e.g. drug, biologic or device) are safe or effective for the purposes under investigation.
  - **3.2.3.** Claims, either explicit or implicit, that the research procedures are known to be equivalent or superior to other interventions off-study.
  - **3.2.4.** Terms such as "new treatment", "new medication", or "new drug".
  - **3.2.5.** Promises of "free medical treatment" regardless of whether the treatment will be provided without charge.
  - **3.2.6.** A stated amount of compensation for participation (monetary or related to free or reduced price for services), or indication that compensation is available, in any font, font size, or manner that is intended to draw attention to the value or availability of compensation.
  - **3.2.7.** Any exculpatory language.
  - **3.2.8.** Make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling.

## 4.0 Printed Advertisement

- **4.1.** All printed advertisements developed by the investigator or staff, or developed by an outside sponsor must be uploaded to RSS (except when the Organization is relying on another IRB as the IRB of record), and reviewed and approved by the IRB.
- **4.2.** Printed advertisement must include the following items:
  - **4.2.1.** Name and address of the PI and associated institution.
  - **4.2.2.** A clear statement that the activity is research.
  - **4.2.3.** Purpose of the research
  - **4.2.4.** IRB number
- **4.3.** Printed advertisement may include the following information, as appropriate:
  - **4.3.1.** Brief relevant eligibility criteria (e.g., why a person might believe he/she is a potential subject)
  - **4.3.2.** Time or other commitments required from the subject, including number of study visits and duration of the study.
  - **4.3.3.** A brief list of potential benefits to the subject, and of risks and discomforts, if any. If potential benefits are stated in recruitment material then the risks must also be stated.
  - **4.3.4.** Location of the research, contact person, and phone number for further information.
- **4.4.** The layout of the advertisements must conform to the Organization's requirements regarding the use of logos and brands.
- **4.5.** It is the responsibility of the investigator to ensure that the final published copy (including font and size) matches that approved by the IRB.
- **4.6.** When accrual to the research is completed, the investigator is responsible for terminating newspaper or magazine ads.

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## 5.0 Radio and Television Advertisements

- **5.1.** Radio and Television advertisement must include the following items: 5.1.1. Name of the PI and associated institution. 5.1.2. A clear statement that activity is research. 5.1.3. Purpose of the research.
- **5.2.** Radio and Television advertisement may include the following information, as appropriate:
  - **5.2.1.** Brief relevant eligibility criteria (e.g., why a person might believe he/she is a potential subject).
  - **5.2.2.** Time or other commitments required from the subject
  - **5.2.3.** A brief list of potential benefits to the subject, and possible risks and discomforts, if any. Per FDA Guidance, if potential benefits are stated in recruitment material then the possible risks must also be stated.
  - **5.2.4.** Location of the research, contact person, and phone number for further information.
- **5.3.** It is the responsibility of the investigator to ensure that the final broadcast matches that approved by the IRB.
- **5.4.** When accrual to the research is completed, the investigator is responsible for assuring that radio or television ads cease.

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## 6.0 Electronic Advertisements (including social media or other on-line venue)

- **6.1.** Electronic advertisement must include the following items:
  - **6.1.1.** Name and address of the PI and associated institution.
  - **6.1.2.** A clear statement that the activity is research.
  - **6.1.3.** Purpose of the research
  - **6.1.4.** IRB number
- **6.2.** Electronic advertisement may include the following information, as appropriate:
  - **6.2.1.** Brief relevant eligibility criteria (e.g., why a person might believe he/she is a potential subject).
  - **6.2.2.** Time or other commitments required from the subject.
  - **6.2.3.** A brief list of potential benefits to the subject, and possible risks and discomforts, if any. Per FDA Guidance, if potential benefits are stated in recruitment material then the possible risks must also be stated.
  - **6.2.4.** Location of the research, contact person, and phone number for further information.
  - **6.2.5.** A link (and/or a URL) pointing to a site maintained by the Organization.

    - **6.2.6.** A link (and/or a URL) pointing to a site maintained by an external organization with the domain “org”, “edu” or “gov”, that is relevant to the disease or condition which is being studied, or to the practice of human subject research or protection of human research subjects in general.
- **6.3.** It is the responsibility of the investigator to ensure that the final published copy (including font and size) matches that approved by the IRB.
- **6.4.** If the advertisement includes a link or a URL, it is the responsibility of the investigator to regularly check that link to be assured that it remains intact.
- **6.5.** When accrual to the research is completed, the investigator must disable study-specific electronic advertising

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## 7.0 Submission and Review of Advertisements

- **7.1.** Final versions of all advertisements including print media, audio scripts for radio, video scripts for television, and screenshots of online advertising (including all webpages linked to the advertisement) related to research for which the UNMC IRB is the IRB of record, must be submitted to the ORA in accordance with HRPP policy 2.1 (Submission of Items for Review) for review and approval. Copies will be maintained by the ORA.
    - **7.1.1.** Submission of planned advertising to the ORA must include a description of the location the advertisement will be placed (that is, the name of the publication {e.g., the Omaha World-Herald}, the specific media outlet {e.g., KETV} and/or the website or venue {e.g., specific Facebook page or community}), and the expected duration of the advertising.
    - **7.1.2.** The final version of any advertisement may be reviewed by either the full IRB or by the expedited method if it qualifies in accordance with 45 CFR 46.110(b) and HRPP policies 2.2 (Full IRB Review) and HRPP policies 2.3 (Expedited Review).
    - **7.1.3.** The IRB approval letter will cite the approved version of the advertisement.
- **7.2.** Advertisements related to research for which the Organization is relying on another IRB as the IRB of record need not be submitted to the ORA for review, unless such review is requested by the investigator or by the reviewing IRB.

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Revised 9/9/2022 – Clarified that advertisements related to research for which the Organization is relying on another IRB as the IRB of record, must be adhere to this policy; however, the ORA will not routinely review such advertising unless requested to do so by the investigator or the reviewing IRB. {Approved Chris Kratochvil (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

Revised 9/15/2022 – removed requirement that printed advertisements be prepared within RSS (functionality not yet implemented). {Approved Chris Kratochvil (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

Revised 10/12/2022 - emphasized what information “must” be included vs “may” be included, in advertisements {Approved Chris Kratochvil (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

Board Notified: 11/29/2022

Revised: 12/1/2022 - typo corrected in 7.0 (Robert Lewis - IRB Assoc)

Revised: 3/29/2023 - typos corrected in Section 2.0 and section numbering corrected 2.1-2.4 (Robert Lewis - IRB Assoc)

# 3.6 Subject Recruitment Through Direct Invitation

## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for subject recruitment through direct invitations to participate.
Subject recruitment through advertisements is described in HRPP policy 3.5.

## 2.0 Policy

- **2.1.** It is the policy of the Organization that all direct recruitment materials must be reviewed and approved before they can be used to recruit potential subjects.
- **2.2.** It is the policy of the Organization that recruitment materials be clear, promote equitable enrollment and not represent undue influence or coercion.
- **2.3.** It is the policy of the Organization that direct recruitment of subjects to research be respectful of the privacy of potential subject.

## 3.0 Definitions

- **3.1.** ***"Opt-In"*** designation refers to agreement by the patient to be contacted for possible inclusion in biomedical research based on information in the patient's EMR, as reflected in the UNMC/Nebraska Medicine [UNMC/NM] "Conditions of Treatment Form" (or, when available, the Children's Hospital Medical Center [CHMC] "Conditions of Treatment Form").
- **3.2.** ***Honest Broker*** refers to a person, appropriately trained and designated by the Organization, whose responsibility is to de-identify protected health information and provide that de-identified information to investigators, in accordance with UNMC policy 6074.

## 4.0 Invitations to Patients

- **4.1.** This section applies to patients (present and former) associated with UNMC/NM (including hospital and/or clinics), Bellevue Medical Center, or CHMC (including Children's Physicians Clinics).
- **4.2.** Distribution Lists based on Clinical Databases or Prior Research Subject Databases
  - **4.2.1.** Potential subjects listed in these databases are either: (1) current or former patients of the investigator; or (2) patients to whom he/she has ethical access per HRPP policy 3.12 (Ethical Access); or (3) previous research subjects who have given express permission (usually as part of an IRB approved consent process) to be listed in the database for the purpose of being contacted for future research studies.
- **4.3.** Distribution Lists based on the Conditions of Treatment Form designation ("opt-in" designation)
  - **4.3.1.** The Associate Vice Chancellor must approve subject recruitment plans, which include directed invitations to former or present patients based on the Conditions of Treatment Form designation ("opt-in designation) for Clinical Research.
  - **4.3.2.** Once approved by the Associate Vice Chancellor for Clinical Research, the study personnel can add this documentation to their IRB submission.
  - **4.3.3.** After review and approval by the IRB, the Director of Electronic Health Record Access Core will authorize an "honest broker" to generate the distribution list based on the inclusion parameter defined in the Request for Electronic Health Data Form.
  - **4.3.4.** Only patients who have opted-in to be contacted for research on his/her Conditions of Treatment Form may be included in this search.
  - **4.3.5.** Once the distribution list is provided, it must be kept on a secure/encrypted UNMC/NM computer (reference End User Device Security procedure or IM16 End User

Device Policy) for no more than 3 months. After that time, the distribution list must be re-run to validate the opt-in recruitment status.
    - **4.3.6.** The list must be deleted/destroyed once it is no longer in use (Nebraska Medicine policy IM14-Destruction of Confidential Information).
    - **4.3.7.** Patients who have opted-out based on the Conditions of Treatment Form designation may still be contacted if they are either: (1) current or former patients of the investigator, or (2) patients to whom the investigator has ethical access per HRPP policy 3.12 (Ethical Access); or (3) previous research subjects who have given express permission to be contacted for future research studies.
    - **4.3.8.** Note that currently CHMC and Children's Physicians clinics do not utilize an "opt-in" designation on the Conditions of Treatment form; therefore Distribution Lists based on the Conditions of Treatment Form designation described in this section (3.1) do not apply for potential subjects from those sites.
- **4.4.** No more than three invitation attempts between all media channels (phone, mail, e-mail) for any specific study may be made from any Distribution List described above unless specific approval is given by the IRB or by the expedited reviewer as applicable. Specific parameters regarding frequency are noted below.
- **4.5.** Contacting Patients by Email via MS Outlook (or future email system supported by the Organization)
    - **4.5.1.** If multiple recipients are included on the same email, the blind copy email function must be used to prevent recipients from seeing the email address of another subject or potential subject.
    - **4.5.2.** Emails must contain minimal PHI, limited to (a) Patient name, and (b) email address.
    - **4.5.3.** The subject line must clearly identify "UNMC/Nebraska Medicine (or CHMC) Research Opportunity". PHI or study information must not be contained in the subject line.
    - **4.5.4.** The sender of the email must be clearly identified as affiliated with the Organization
    - **4.5.5.** The text of the email must include only the following items:
        - **4.5.5.1.** Name and email address of the PI and associated institution.
        - **4.5.5.2.** A clear statement that activity is research.
        - **4.5.5.3.** Purpose of the research.
        - **4.5.5.4.** IRB number.
        - **4.5.5.5.** An invitation to contact the investigator for more information, with telephone number if applicable.
        - **4.5.5.6.** An explanation that the patients name and contact information were available because they had chosen to opt-in to be contacted for research on his/her Conditions of Treatment Form.
        - **4.5.5.7.** Information for the patient on how to change their research recruitment option in the conditions of treatment form and the contact information for the Research Subject Advocate.
    - **4.5.6.** Email invitations to UNMC/NM or BMC patients obtained through the Conditions of Treatment Distribution lists must be sent by the Clinical Research Outreach Coordinator (or equivalent position), via a central email address.
    - **4.5.7.** The Pediatric Research Office (PRO), via a central email address, must send email invitations to CHMC patients.
    - **4.5.8.** The reply back to sender will be reviewed by the Clinical Research Outreach Coordinator or the PRO coordinator, and then forwarded to research staff if appropriate.
    - **4.5.9.** The recruitment email invitation may be sent to potential subjects no more often than weekly unless specifically authorized by the IRB.
    - **4.5.10.** If a potential subject declines participation in a specific study, no further recruitment emails may be sent regarding that study.
- **4.6.** Contacting Patients by EPIC Email through One Chart
    - **4.6.1.** The subject line must clearly identify "UNMC/Nebraska Medicine (or CHMC) Research Opportunity". PHI or study information must not be contained in the subject line.
    - **4.6.2.** The reply back to sender will be set to return all replies regarding recruitment to the investigator with ethical access.
    - **4.6.3.** The text of the email must include only the following items:
        - **4.6.3.1.** Name and email address of the PI and associated institution.
        - **4.6.3.2.** A clear statement that activity is research.

        - **4.6.3.3.** Purpose of the research.
        - **4.6.3.4.** IRB number.
        - **4.6.3.5.** An invitation to contact the investigator for more information, with telephone number if applicable.
    - **4.6.4.** The recruitment email invitation may be sent to potential subjects no more often than weekly unless specifically authorized by the IRB.
    - **4.6.5.** If a potential subject declines participation in a specific study, no further recruitment emails may be sent regarding that study.
- **4.7.** Contacting Patients by Phone
    - **4.7.1.** Telephone script must be approved by the IRB prior to use.
    - **4.7.2.** Recorded voice messages must go through the Clinical Research Outreach Coordinator (or equivalent position).
    - **4.7.3.** Frequency and number of calls must be specified by the investigator in the IRB application, and must be approved by the IRB.
    - **4.7.4.** If voicemails are left the message may only state that the call is about a research study for which the patient may be eligible and offer a call back number. The voicemail must not provide any additional details regarding the trial or the reason a patient may be eligible.
    - **4.7.5.** If a potential subject declines participation in a specific study, no further recruitment phone calls may be made regarding that study.
    - **4.7.6.** All recorded messages must follow the Telephone Consumer Protection Act.
- **4.8.** Contacting Patients by Mail
    - **4.8.1.** Letters must contain minimal PHI, limited to (a) Patient name and (b) address.
    - **4.8.2.** All materials should be in an envelope with only patient's name and address; the return address must include the Organization name, but no specific medical or surgical department.
    - **4.8.3.** If postcard format is appropriate, the postcard must fold and seal to cover any medical/trial information.
    - **4.8.4.** The text of the letter must include only the following items:
        - **4.8.4.1.** Name and email address of the PI and associated institution.
        - **4.8.4.2.** A clear statement that activity is research.
        - **4.8.4.3.** Purpose of the research.
        - **4.8.4.4.** IRB number.
        - **4.8.4.5.** An invitation to contact the investigator for more information, with telephone number if applicable.
        - **4.8.4.6.** An explanation of how the patients name and contact information were available to the investigator (for example, because they had chosen to opt-in to be contacted for research on his/her Conditions of Treatment Form, or because he/she had previously participated in research and had agreed to be contacted regarding additional research studies).
        - **4.8.4.7.** If the patient had chosen to opt-in to be contacted for research on his/her Conditions of Treatment Form, information on how to change their research recruitment option, and the contact information for the Research Subject Advocate.
    - **4.8.5.** The recruitment letter may be sent to potential subjects no more often than weekly unless specifically authorized by the IRB.
    - **4.8.6.** If a potential subject declines participation in a specific study, no further recruitment letters may be sent regarding that study.

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## 5.0 Invitations to Prospective Subjects who are not Patients

This section applies to prospective subjects who may be eligible for participation in research but who are not primarily eligible because they have a disease or condition being diagnosed or treated at UNMC/Nebraska Medicine (including hospital and/or clinics), Bellevue Medical Center, or Children's Hospital & Medical Center (including Children's Physicians Clinics). They may be patients or former patients, but that is not the primary reason they may be eligible.

*Note: Examples of this subject population would be public or private school students; college, trade or professional school students (e.g., UNO freshman, enrollees at a particular trade school, UNMC SOM*

*students); cultural, ethnic or religious groups (e.g., Sudanese immigrants, members of a particular church); trades or professions (e.g., farmers, physicians, prison guards).*

- **5.1.** Creation of Distribution Lists
  - **5.1.1.** In most cases, unless the investigator has ethical access to names of potential subjects, or the names are obtained from publicly available databases, the distribution list must remain within the group, which has generated the list (that is, the investigator should not have access to the names or contact information on the list). The invitation to participate should come from the group, which generated the list.
  - **5.1.2.** In certain circumstances, when the group supplying the list cannot or will not be responsible for sending the invitation, the IRB may specifically approve that the list be transferred to the investigator. In making this exception, the IRB must be satisfied that:
    - **5.1.2.1.** The risks of disclosure of the contact information constitutes no more than minimal risk to potential subjects (for example, disclosure would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation), and
    - **5.1.2.2.** There are adequate safeguards to minimize the risk of disclosure beyond the investigator and study personnel, and
    - **5.1.2.3.** There are adequate provisions to protect the privacy of subjects.
  - **5.1.3.** If the distribution list is provided to the investigator, it must be kept on a secure computer for no more than 3 months. The list must be deleted/destroyed once it is no longer in use (Nebraska Medicine policy IM14: Destruction of Confidential Information).
  - **5.1.4.** All information distributed to the investigator must be in compliance with applicable privacy laws and regulations, including The Family Educational Rights and Privacy Act (FERPA) (20 U.S.C. § 1232g; 34 CFR Part 99).
- **5.2.** Contacting Prospective Subjects by Email
  - **5.2.1.** As noted above, in most cases the invitation to participate should come from the group, which generated the list. If the invitation comes directly from the investigator (as per section 5.2.2 above) emails must be sent from a UNMC/Nebraska Medicine, UNO, or CHMC, Outlook account.
  - **5.2.2.** If multiple recipients are included on the same email, the blind copy email function must be used to prevent recipients from seeing the email address of another potential subject.
  - **5.2.3.** The subject line must clearly identify UNMC, UNO or CHMC "Research Opportunity". Study information must not be contained in the subject line.
  - **5.2.4.** The group sending the email must be clearly identified.
  - **5.2.5.** The affiliation of the investigator with the Organization must be clearly stated in the email.
  - **5.2.6.** The email must include an explanation why the prospective subject's name and contact information were available.
  - **5.2.7.** The text of the email must include only the following items:
    - **5.2.7.1.** Name and email address of the PI and associated institution.
    - **5.2.7.2.** A clear statement that activity is research.
    - **5.2.7.3.** Purpose of the research.
    - **5.2.7.4.** IRB number.
    - **5.2.7.5.** An invitation to contact the investigator for more information, with telephone number if applicable.
    - **5.2.7.6.** A description of why the prospective subject's name and contact information were available.
  - **5.2.8.** The recruitment email invitation may be sent to potential subjects no more often than weekly unless specifically authorized by the IRB.
- **5.3.** Contacting Prospective Subjects by Phone
  - **5.3.1.** Telephone script must be approved by the IRB prior to use.
  - **5.3.2.** Frequency and number of calls must be specified by the investigator in the IRB application, and must be approved by the IRB.
  - **5.3.3.** If voicemails are left, the message may only state that the call is about a research study for which the patient may be eligible and offer a call back number. The voicemail must not provide any additional details regarding the trial or the reason a prospective

subject may be eligible.
    - **5.3.4.** All recorded messages must follow the Telephone Consumer Protection Act.
- **5.4.** Contacting Prospective Subjects by Mail
    - **5.4.1.** All materials should be in an envelope with only prospective subject's name and address; the return address must include the Organization name (if sent by the investigator), or the name of the group supplying the distribution list.
    - **5.4.2.** The affiliation of the investigator with the Organization must be clearly stated in the letter.
    - **5.4.3.** The mail must include an explanation why the prospective subject's name and contact information were available.
    - **5.4.4.** The text of the letter must include only the following items:
        - **5.4.4.1.** Name and email address of the PI and associated institution.
        - **5.4.4.2.** A clear statement that activity is research.
        - **5.4.4.3.** Purpose of the research
        - **5.4.4.4.** IRB number
        - **5.4.4.5.** An invitation to contact the investigator for more information, with telephone number if applicable.
        - **5.4.4.6.** A description of why the prospective subject's name and contact information were available.
    - **5.4.5.** The recruitment letter may be sent to potential subjects no more often than weekly unless specifically authorized by the IRB.

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DOCUMENT HISTORY:

Written: 8/23/2018 (Approved: 8/23/2018) - original author not recorded

# 3.7 Finder's Fees and Recruitment Bonuses

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements related to finder's fees and recruitment bonuses.

## 2.0 Policy

HHS regulations at 45 CFR 46.116 and FDA regulations at 21 CFR 56.116 require minimization of the possibility of coercion or undue influence. It is the view of the Organization that payment of finder's fees or recruitment bonuses to investigators or to any representative of the Organization may create the perception that subjects or potential subjects could be unduly influenced or coerced to participate (or continue participation). Therefore, it is the policy of the Organization that such payments are not permitted.

## 3.0 Definitions

- **3.1.** Finder's Fee: Payment made by an investigator or sponsor to an organization or individual (including non-research personnel or a research participant) for identifying and/or referring potential participants for research.
- **3.2.** Recruitment Bonus: Payment, merchandise, or other gift or service offered by a sponsor as an incentive or reward to an organization, investigator, or investigator's staff designed to accelerate recruitment that is tied to enrollment rate, timing, or numbers.

## 4.0 Finder's Fees

- **4.1.** Finder's fees, which are paid to investigators, investigator's staff or to any representative of the Organization, for referring prospective research subjects, are not permitted.
- **4.2.** Finder's fee which are paid to non-research personnel or to research subjects for referring additional subjects are generally not permitted. Under limited circumstances the IRB may approve the payment of small amounts if such payment is necessary to recruit a population of subjects who would potentially benefit from the research, but would otherwise be difficult to recruit.

## 5.0 Recruitment Bonuses

- **5.1.** Recruitment bonuses which are tied to the enrollment of a set number of subjects or accelerated enrollment, are not permitted.

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# 3.8 Research Subject Compensation and Reimbursement

## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements and limitations regarding compensation and reimbursement of research subjects.

## 2.0 Policy

It is the policy of the Organization that

- 2.1. Compensation for research subjects may be acceptable if 1) the possibility of undue influence is minimized, and 2) the compensation is considered reasonable payment for time spent, or, if minimal risk research, a reasonable incentive for participation.
- 2.2. Compensation in any form is not considered a benefit to be weighed against risks in the IRB's assessment of the risk/benefit relationship of the research, and that compensation may not be presented to the potential subject as a benefit in either the process of consent, or the potential benefits section of the consent form.
- 2.3. Reimbursement for study-related travel and out of pocket expenses is acceptable.
- 2.4. Investigators should attempt to minimize financial sacrifice on the part of subjects and, as possible and appropriate, offer equitable reimbursement for costs.

## 3.0. Definitions

- 3.1. Compensation refers to monetary or other payment to the subject primarily intended to compensate for time spent in participating in the research activities, but also, in limited circumstances, as incentive to participate.
- 3.2. Reimbursement refers to monetary payment to offset expenses incurred as a direct result of participating in research activities. This includes travel expenses, lodging, meals, daycare, and may also include specific costs associated with research interventions (for example, costs of medications or therapies).

## 4.0. General Principles

- 4.1. Compensation for participation in research is not a requirement.
- 4.2. The amount or type of compensation should not serve as undue inducement to potential subjects.
- 4.3. For research posing greater than minimal risk to subjects, the amount of compensation should reflect the amount of time required of the subject. The amount of compensation should not be tied to the degree of risk or discomfort associated with the study.
- 4.4. For research posing minimal risk to subjects, since the risks associated do not exceed those of daily life or routine physical or psychological examination, compensation is not an inducement to offset risk. Therefore, compensation for minimal risk research may represent a reasonable incentive for participation.
- 4.6. Reimbursement for expenses is not a requirement; however, participation in research should, if possible, not require any financial sacrifice on the part of the subject. Investigators must provide adequate justification for failure to reimburse reasonable expenses.
- 4.7. The IRB will consider the financial burden imposed on subjects as a consequence of participating in the research when evaluating whether risks are minimized and whether the risk-benefit relationship of the research is acceptable.

## 5.0 Specific Requirements for Compensation

- 5.1. Compensation for research which involves greater than minimal risk should be based on a reasonable hourly wage for time spent in preparation for, participation in, and recovery from, research interventions. A reasonable hourly rate is $25.00 per hour.
- 5.2. Research interventions include (but are not limited to) procedures performed, visits to a clinic or research setting, phone interviews, or surveys completed.
- 5.3. If appropriate, hourly compensation should include all parties involved. For example, if a family member is required to be present to drive a research subject home after a procedure, their time may be included in determining appropriate compensation.
- 5.4. Compensation above these levels must be specifically justified by the investigator and must comply with the general principles described in Section 4.0 of this policy.
- 5.5. The IRB has the authority to review the level of compensation and, in appropriate circumstances, limit or increase the total value.
- 5.6. The terms of the compensation must be disclosed in the IRB application and ICF, and discussed during the informed consent process, but the total amount of compensation should not be emphasized.
- 5.7. Compensation to subjects must be prorated based upon the duration of participation of the subject in the research. Any credit for payment should accrue as the study progresses and may not be contingent upon the subject completing the study. If a subject does not complete the study, prorated payments should be made regardless of whether withdrawal was voluntary (subject decided to withdraw from the study) or involuntary (based on withdrawal criteria of the research protocol.). Prorated compensation should be provided, if possible, to subjects at defined intervals as opposed to at the end of a study.
- 5.8. Subjects may be paid in any manner consistent with Business & Finance policies of the relevant component of the Organization (UNMC, UNO, CN, NM, BMC). However, within acceptable payment mechanisms, the IRB or expedited reviewer may require a particular method in order to minimize risks or provide equitable compensation.
- 5.9. The IRB does not allow bonuses to be paid for completion of a study, as it may unduly influence a subject to continue in a study when they would otherwise have chosen to withdraw.
- 5.10. Compensation for participation in research may not include free samples or coupons good for a discount on the purchase price of the test product upon conclusion of the study. The IRB views this form of compensation to be an inappropriate marketing tool when associated with research participation.
- 5.11. For studies where compensation is likely to total more than $600, the consent form must include a statement that an IRS form 1099 will be issued if the total compensation from participation in research reaches $600 in any given year.

- 5.12. Records should be maintained at the department or other level that tracks all forms of compensation and their distributions. The amount and type of compensation must be able to be tracked to a corresponding recipient. If the accounting and/or payment office required the subject to provide their Social Security Number, this must be both justified and disclosed in the consent form.
- 5.13. Monetary payments for involvement of young children <7 years of age in research should not be made directly to the minor (though parents may still be compensated as above). It may be appropriate to offer young children an age-appropriate token for their participation, such as a small toy. Direct payment to older children (7-12 years) may be made with appropriate justification. Adolescents (>13 years) may be directly compensated.
- 5.14. Due to the concerns relating to the potential subject's overestimating the value of compensation the UNMC IRB will not allow the use of a lottery (or raffle) as a mechanism to provide compensation to subjects for participation in greater than minimal risk research.

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# 6.0. Requirements for Reimbursement

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- 6.1. Any costs to the subject that may result from participation in the research must be justified and disclosed in the consent form.
- 6.2. The terms of the reimbursement must be disclosed in the IRB application and ICF and discussed during the informed consent process.
- 6.3. Any reimbursement for costs incurred by subjects must be equitable, based on actual or reasonably estimated costs.
- 6.4. Eligibility for reimbursement for travel associated expenses may not be contingent on arbitrary distance threshold (that is, investigators may not offer reimbursement only for subjects who travel more than X miles).
- 6.5. The preferred form of reimbursement to subjects is a Cash Debit Card; however, subjects may be reimbursed in any manner consistent with Business & Finance policies of the relevant component of the Organization (UNMC, UNO, CN, NM, BMC), or with the terms of a Clinical Trial Agreement as applicable.

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POLICY AMENDED: Revised June 25, 2021 Separated policies and requirements for compensation (payment) from reimbursement, and reorganized policy accordingly; included definitions of above; explicitly stated that investigators should attempt to minimize financial sacrifice on the part of subjects and, as possible and appropriate, offer equitable reimbursement for costs; explicitly stated that compensation for minimal risk research may represent a reasonable incentive for participation (previously implied since no restriction placed on payment for minimal risk research); added prohibition that reimbursement for travel associated expenses may not be contingent on distance; specified preferred mechanism for compensation and reimbursement; allowed for direct payment to adolescents (and older children with justification).

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Revised: 8/31/2021 - Separated policies and requirements for compensation (payment) from reimbursement, and reorganized policy accordingly; included definitions of above; explicitly stated that investigators should attempt to minimize financial sacrifice on the part of subjects and, as possible and

appropriate, offer equitable reimbursement for costs; explicitly stated that compensation for minimal risk research may represent a reasonable incentive for participation (previously implied since no restriction placed on payment for minimal risk research); added prohibition that reimbursement for travel associated expenses may not be contingent on distance; specified preferred mechanism for compensation and reimbursement; allowed for direct payment to adolescents (and older children with justification).

Revised: 6/5/2023 - Revised section 5.2 to allow the IRB has the authority to review the level of compensation and, in appropriate circumstances, limit or increase the total value; revised section 5.7 to delete preferred method of payment (preferred method will be decided by B&F; revised section 5.7 to allow, within acceptable payment mechanisms, the IRB or expedited reviewer may require a particular method in order to minimize risks or provide equitable compensation.

Revised: 8/12/2023 - Clarified that section 6.4 refers to an “arbitrary distance threshold”; minor grammatical changes. {Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

7/3/2024 – increased hourly compensation from $20/hour to $25/hour (section 5.1); clarified that “research interventions” included, but were not limited to, the example provided in section 5.2; deleted requirement for individual IRB Executive Chair/designee approval of use of a lottery (or raffle) as a mechanism to provide compensation to subjects for participation in minimal risk research; minor stylistic changes. {Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

# 3.9 Contraception Requirements

## 1.0 Purpose

The purpose of this policy and procedure is to describe the contraception requirements for subjects participating in research.

## 2.0 Policy

It is the policy of the Organization that subjects must utilize appropriate contraception methods while participating in research with potential for reproductive toxicity.

- **2.1.** Contraception requirements should be based on the FDA Pregnancy and Lactation Labeling Rule (for all investigational drug applications submitted after 6/30/2015). Drugs approved prior to 6/30/2015 contraception requirements may be based on FDA Use-in-Pregnancy Category until Pregnancy and Lactation Labelling has been submitted and approved by FDA.
- **2.2.** Female study volunteers who are not of reproductive potential (premenarchal, postmenopausal, or surgically or otherwise sterile) are eligible to participate in research without requiring the use of contraception.
- **2.3.** Male research subjects, including those who have undergone successful vasectomy with resulting azoospermia or have azoospermia for any other reason, should use barrier contraception, or their partners should use appropriate contraception, unless the agent has been shown not to be present in seminal fluid, or the agent has been shown to have no genotoxic, reproductive, or developmental effects in nonclinical or clinical studies.
- **2.4.** It is the responsibility of the investigator with or without the Research Subject Advocate, to discuss the risks and benefits of each form of contraception with potential study participants to ensure that subjects are making an informed choice.

## 3.0 Categories based on FDA Pregnancy and Lactation Labeling Rule (PLLR)

- **3.1.** ***Group 1:*** No systemic absorption of drug or biologic.
- **3.2.** ***Group 2:*** Review of clinical trials conducted in pregnant women, pregnancy exposure registries, and other large scale epidemiologic studies show no evidence of adverse developmental outcomes.
- **3.3.** ***Group 3:*** In the absence of human data, animal studies show no evidence of adverse developmental outcomes.
- **3.4.** ***Group 4:*** Animal studies show evidence of adverse developmental outcomes, at dose levels higher than those to be used in this study.
- **3.5.** ***Group 5:***
  - **3.5.1.** Review of clinical trials conducted in pregnant women, pregnancy exposure registries, other large scale epidemiologic studies, or well described case-series show evidence of adverse developmental outcomes; OR
  - **3.5.2.** Animal studies show evidence of adverse developmental outcomes, at dose levels similar to those to be used in this study; OR
  - **3.5.3.** The mechanism of action of the drug suggests the possibility of adverse developmental outcomes.

## 4.0 Definitions of the FDA Use-In-Pregnancy Categories

- **4.1.** ***Category A: Controlled studies show no risk:*** Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.

- **4.2. *Category B: No evidence of risk in humans*** Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals nor, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.
- **4.3. *Category C: Risk cannot be ruled out:*** Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk.
- **4.4. *Category D: Positive evidence of risk:*** Studies in humans, or investigational or post-marketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
- **4.5. *Category X: Contraindicated in pregnancy:*** Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk that clearly outweighs any possible benefit to the patient.

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## 5.0 Procedure

- **5.1.** For drugs or biologics for which there is Pregnancy and Lactation Labelling available (all investigational drug applications submitted after 6/30/2015, and all approved drugs for which Pregnancy and Lactation Labelling has been submitted and approved by FDA), the ICFs must include the appropriate standard contraception language based upon the categories in section 3.0 (see Addendum 1 attached at the end of this policy).
  - **5.1.1. *Studies Involving Group 1 Drugs***
    - **5.1.1.1.** Protocol may not require use of contraception. Exceptions to this policy must be approved by the full IRB after adequate justification by the PI.
  - **5.1.2. *Studies involving Group 2 Drugs*** (Human data shows no evidence of adverse developmental outcome)
    - **5.1.2.1.** The protocol may require the use of ONE form of contraception, with IRB approval, after justification by the PI.
  - **5.1.3. *Studies involving Group 3 Drugs*** (Animal Data shows no evidence of adverse developmental outcome)
    - **5.1.3.1.** The protocol may require the use of ONE form of contraception, with IRB approval, after justification by the PI.
  - **5.1.4. *Studies involving Group 4 Drugs*** (Animal studies show evidence of adverse developmental outcomes, at dose levels higher than those to be used in this study)
    - **5.1.4.1.** The protocol must require the use of ONE or TWO form(s) of concurrent contraception.
  - **5.1.5. *Studies involving Group 5 Drugs*** (Animal or Human studies show evidence of adverse developmental outcomes, or drug mechanism of action suggests the possibility of adverse developmental outcomes)
    - **5.1.5.1.** The protocol must require the use of TWO forms of concurrent contraception.
  - **5.1.6.** For all groups, the ICF must utilize the appropriate standard language.
  - **5.1.7.** The duration of contraception must be stated in the IRB Application and in the ICF. If contraception is required for longer than the time the drug is being administered, justification must be provided.
- **5.2.** For drugs or biologics for which Pregnancy and Lactation Labeling is not available, the ICFs must include the appropriate standard contraception language based upon the categories in section 4.0 (see Addendum 1 attached at the end of this policy).
  - **5.2.1. *Studies Involving Category A Drugs:***
    - **5.2.1.1.** Protocol may not require use of contraception. Exceptions to this policy must be approved by the full IRB after adequate justification by the PI.
  - **5.2.2. *Studies Involving Category B Drugs:***
    - **5.2.2.1.** The protocol may require the use of ONE form of contraception, with IRB approval, after justification by the PI.
  - **5.2.3. *Studies Involving Category C Drugs:***
    - **5.2.3.1.** The protocol must require the use of ONE or TWO form(s) or concurrent

contraception.
    - **5.2.4.** ***Studies Involving Category D Drugs:***
        - **5.2.4.1.** The protocol must require the use of TWO forms of concurrent contraception.
    - **5.2.5.** ***Studies Involving Category X Drugs:***
        - **5.2.5.1.** The protocol must require the use of TWO forms of concurrent contraception.
- **5.3.** For all groups and categories described above, the ICF must use the corresponding standard Contraception language in Addendum 1, except:
    - **5.3.1.** For Group 5 drugs, or category D or X drugs, if the sponsor mandates specific contraception language be included in the ICF this language may be used in lieu of the standard language in Addendum 1, provided the IRB determines that the specified language is as protective of the potential fetus, and does not create undue burden on the mother.
- **5.4.** If PI wishes to list specific forms of birth control in any of the above categories (rather than the generic "appropriate method(s) of birth control" found in the IRB-approved template), the list must include at least (1) condoms (male or female) with or without a spermicidal agent and (2) diaphragm or cervical cap with spermicide, unless the sponsor/PI presents justification that any of these are medically or scientifically inappropriate considering both the nature of the research and the subject population.
- **5.5.** The IRB Executive Chair, on behalf of the IRB Executive Committee, is authorized to negotiate with sponsors and/or PIs to address requests for specific language modifications in the ICF provided the requested modifications are at least as protective as the requirements found in the IRB-approved template.

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## ADDENDUM #1

ICF Pregnancy Risk Statements

### *Category A or Group 1 drugs:*

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions

### *Category B or Group 2 or Group 3 drugs when contraception is NOT required:*

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

### *Category B or Group 2 or Group 3 drugs when contraception IS required:*

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test before entering the study [and before each treatment – as appropriate].

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use ONE appropriate method of birth control every time you have sex, or you must not have sex.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to use birth control to avoid pregnancy for X months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for X months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

### *Category C or Group 4 drugs:*

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test before entering the study [and before each treatment – as appropriate].

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use ONE [or TWO] appropriate method(s) of birth control every time you have sex, or you must not have sex.

Because of the possible risk to the fetus [OR an unborn child], methods of natural family planning are not, by themselves, reliable enough to avoid pregnancy.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to use birth control to avoid pregnancy for X months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for X months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

### *Category D or Group 5 Drugs:*

PREGNANCY RISKS It is possible that the medicines used in this study could injure a fetus [OR an unborn child] if you, or your partner, become pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test before entering the study [and before each treatment – as appropriate].

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use TWO appropriate methods of birth control every time you have sex, or you must not have sex.

Because of the possible risks to a fetus [OR an unborn child], methods of natural family planning are not, by themselves, sufficiently reliable to avoid pregnancy.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to use birth control to avoid pregnancy for X months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for X months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

### *Category X Drugs:*

**Since studies of the drug in humans, or investigational or post-marketing data, have demonstrated fetal risk, contraception is required and the language must be at least as protective as Category D language above. If the sponsor or FDA require inclusion of specific language relating to fetal risk, monitoring for pregnancy and prevention of pregnancy in the ICF, it may be included, and redundant category D language deleted.**

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# 3.10 Pregnancy Testing

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for determining how and when pregnancy testing should be performed on subjects who are of childbearing potential enrolled in protocols that describe pregnancy as an exclusion criterion.

## 2.0 Policy

It is the policy of the Organization that when women of childbearing potential are enrolled in protocols which include a pregnancy exclusion criterion, the protocol must have procedures in place for either pregnancy testing or self-reporting depending on the teratogenic risk.

## 3.0 Definition

- **3.1.** Woman of childbearing potential (WOCBP) for the purpose of this policy is a woman who has begun menstruating and not entered menopause. Women who are sterile due to history of hysterectomy, bilateral oophorectomy, or radical pelvic irradiation are not considered females of childbearing potential.
- **3.2.** Menopause for the purpose of this policy is defined as lack of menses for 12 months in the absence of any reversible medical condition which could produce amenorrhea.

## 4.0 Procedures

- **4.1.** Protocols that describe pregnancy as an exclusion criterion must describe how pregnancy status will be determined.
- **4.2.** Protocols that include an intervention considered potentially harmful to a fetus must include pregnancy testing prior to initiating the intervention(s).
- **4.3.** If pregnancy testing is required (as indicated in Section 4.2 above), testing should be performed on urine unless blood is being drawn for another reason. In that case, serum qualitative pregnancy testing can be performed.
  - **4.3.1.** Quantitative testing is not indicated for the purposes of this policy.
  - **4.3.2.** Acceptable test results are those performed at Nebraska Medicine, BMC, CHMC, or a documented result from the subject's provider.
  - **4.3.3.** Home pregnancy test results are not acceptable.
- **4.4.** Protocols that describe pregnancy as an exclusion criterion, but are not expected to cause fetal harm, may use subject self-report of pregnancy status.
- **4.5.** A negative pregnancy test within 7 days prior to the intervention of interest should be considered current, consistent with Nebraska Medicine Pregnancy Testing Policy (MS72). For ongoing interventions or exposures, testing should be done at a frequency consistent with clinical practice (and not more often than monthly).
- **4.6.** The informed consent/assent process and the ICF must include:
  - **4.6.1.** How often pregnancy testing will be done.
  - **4.6.2.** How often subjects will be informed of results.
  - **4.6.3.** Whether subjects will be removed from the study if they become pregnant.
- **4.7.** Minor subjects should be informed during the consent/assent process and in the ICF that their parent/guardian will be informed of the test results.
- **4.8.** Subjects should be informed of whether they will be charged for pregnancy testing:
  - **4.8.1.** For protocols that require pregnancy testing, but are not expected to cause fetal harm, subjects may not be charged for pregnancy testing.
  - **4.8.2.** The IRB strongly discourages pregnancy testing of females who are NOT of

childbearing potential. However, if such subjects will be tested, they may not be charged for this test.

- **4.9.** Subjects should be given pregnancy test results privately. Minors should be given pregnancy test results privately followed by disclosure by the research team to the subject's parent or guardian.
- **4.10.** Any subject with a positive pregnancy test should be referred to her primary care physician to review the positive test result. Subjects should be offered to have study information sent to their primary care physician if the subject received any intervention prior to the positive pregnancy test.

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# 3.11 Collecting Data from Pregnant Partners of Research Subjects

## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for obtaining informed consent, and collecting data from pregnant partners of research subjects and from their infants.

## 2.0 Policy

- **2.1.** It is the policy of the organization that collection of identifiable private information about the pregnant partner of a research subject, or obtaining data about that subject through interaction with her, constitutes human subject research under 45 CFR 46, and is subject to the requirements of those regulations and of the HRPP.
- **2.2.** It is the policy of the organization that collection of identifiable private information about the infant child (up to 3 months of age) conceived during the time that the mother was a partner of a research subject, or obtaining data about that child through interaction with the child, constitutes human subject research under 45 CFR 46, and is subject to the requirements of those regulations and of the HRPP.

## 3.0 General Considerations

- **3.1.** There is considerable variation between IRBs regarding the interpretation of HHS and FDA regulations in respect to pregnant partners of research subjects. Generally, when the collection of pregnancy outcome data is limited to safety surveillance, neither the pregnant partner nor the infant is considered a human subject under FDA regulations. However, because researchers collect identifiable information about, and interact with, the pregnant partner and/or the infant, the collection of data in this context appears to constitute human subjects research under HHS regulations and the Common Rule.
- **3.2.** Since obtaining pregnancy outcome data involves the use of protected health information of the mother and possibly the infant, the use and sharing of this information is subject to the HIPAA Privacy Rule. Consequently, authorization must be obtained, or waivers of authorization granted, as per regulation and HRPP policies 5.1 (Obtaining Informed Consent form Research Subjects) and 5.2 (Waiver or Alteration of Informed Consent and HIPAA Authorization).
- **3.3.** Collection of pregnancy outcome data that is part of the clinical investigation, or is banked in a pregnancy exposure registry, constitutes human subject research, and is subject to HHS and/or FDA regulations.

## 4.0 IRB Review

- **4.1.** Under most circumstances, protocol for collection of pregnancy outcome data should be submitted to the IRB on a Medical Records Research application.
- **4.2.** If there is a high likelihood that subjects or partners of subjects will become pregnant during the course of the research, the collection of pregnancy outcome data may be included in the initial submission of the protocol.
  - **4.2.1.** The IRB application must include relevant information concerning the pregnant partners and the infant (if applicable) as subject populations distinct from the primary subject of the research. The application must include a thorough description of the specific data to be collected regarding the pregnant partner, and the infant (if applicable), how privacy and confidentiality will be protected, how potential subjects will be identified and recruited, and how informed consent will be sought and documented

- **4.3.** Federally funded research must satisfy requirements of subpart B. Non-Federally funded research must be no more than minimal risk to mother and fetus, and satisfy requirements of HRPP policy 4.2: Research Involving Pregnant Women, Human Fetuses, and Neonates (Nonviable or of Uncertain Viability).
- **4.4.** Federally funded or FDA regulated research must satisfy requirements of subpart D (45 CFR 46.404 and/or 21 CFR 50.51) if information about the infant is collected.
- **4.5.** The Medical Records Research application may be reviewed through an expedited process (per HRPP policy 2.3; Expedited Review) provided it constitutes no more than minimal risk

## 5.0 Informed Consent

- **5.1.** Informed consent must be obtained and documented from the pregnant partner in accordance with HRPP policy 5.1 (Obtaining Informed Consent from Research Subjects).
- **5.2.** If pregnancy outcome data includes identifiable private information regarding the infant, Parental permission must be obtained in accordance with HRPP policy 5.1 (Obtaining Informed Consent from Research Subjects). A separate “Parental Consent Form” is not required; the Pregnant Partner consent form should be structured such that it includes information relevant to the infant, and the partner’s signature on that form signifies her permission

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# 3.12 Ethical Access

## 1.0 Purpose

The purpose of this policy is to define ethical access and to describe the Organization's requirements to protect the privacy of patients in the context of recruitment for participation in research, or for identification of subjects for review of medical records.

## 2.0 Policy

It is the policy of the Organization that obtainment of information about a potential subject, and approach to the potential subject, must occur in a manner that respects the privacy of that person.

## 3.0 Ethical Access for Recruitment of Subjects

For the purposes of this policy, the recruitment of subjects requires two distinct activities, each of which must respect the privacy of patients: (1) obtainment of information about the patient which leads the investigator to believe or conclude that the patient is eligible for the research, and (2) subsequent approach to the patient to explain the research and obtain his/her consent to participate.

- **3.1.** The obtainment of information about the patient which leads the investigator to believe or conclude that the patient is eligible for the research must occur in a manner that does not represent an invasion of his/her privacy. That is, the investigator must have ethical access to clinical information about the patient.
  - **3.1.1.** Ethical access, in this context, may occur in one of three ways:
    - **3.1.1.1.** The researcher has legitimate access to a patient's information for clinical purposes, and therefore has legitimate access to that patient's information for identifying potential research subjects
      Specifically an investigator may have ethical access to this information in this context in one or more of the following manners:
      - **3.1.1.1.1.** The investigator has an ***existing clinical relationship*** with the patient; that is the information has been shared with the clinician for the primary purpose of care of the individual. The patient may or may not know this relationship exists; for example, a specialist consulted informally by the primary provider to assist in the care of the patient may never have met the patient, but the clinical relationship, and hence ethical access exists. Similarly, members of a "care team" (e.g., a hospital pharmacist, or nurse practitioner that rounds with the primary physician provider) have a clinical relationship and therefore ethical access.
        *Note that the "care team" does not usually include a research coordinator acting on behalf of the investigator. However, the IRB or expedited reviewer, or the IRB Chair or Executive Chair may extend "ethical access" to that person under limited circumstances (for example, when the risks associated with loss of confidentiality are low and the information sought is not sensitive). In general, these circumstances would be similar to the conditions of 45 CFR 46.116(d) (or rev 45 CFR 46.116(f)).*
      - **3.1.1.1.2.** The investigator ***works with a provider who has an existing clinical relationship*** with the patient, and the relationship between the investigator and the provider is such that the investigator could reasonably be called upon to care for the patient in a clinical setting. For example, a physician partner of the investigator within the same specialty and clinical group might have the responsibility to care for the patient while on hospital service, or while taking night phone calls. Under these circumstances, for the purpose of this

policy, the investigator has ethical access to information about the patient he/she would reasonably need to know to care for that patient.
        - **3.1.1.1.3.** The investigator's ***professional responsibilities*** (independent of her role as a researcher) require that she has this information. For example, a hospital epidemiologist would have access to a list of inpatients with positive blood cultures, as part of her duties; an Operating Room Nursing supervisor would have a list of names and diagnoses of patients scheduled for surgical procedures on a given day.
    - **3.1.1.2.** The patient has given express consent for investigators to search medical records or other databases to determine potential eligibility (for example, Nebraska Medicine Conditions of Treatment Opt-in for Clinical Research utilizing the Electronic Health Record (EHR) Core).
    - **3.1.1.3.** The IRB has waived the requirement for the patient's consent by finding that the conditions of 45 CFR 46.116(d) (or rev 45 CFR 46.116(f)) are met. Note that waiver of the requirement to obtain the patient's consent to have access to the patient's information to determine eligibility does not imply that, or require that, the requirement for consent to participate in the research is also waived.
- **3.2.** Subsequent approach to the patient to explain the research and obtain his/her consent to participate must also occur in a manner that respects the patient's privacy, and that minimizes the perception of dissemination of private information outside the clinical context (despite "ethical access" as described above.)
  "Approach to the patient" may refer to physical approach to the potential subject (that is, a face-to-face contact), verbal contact (via telephone) or written contact (by letter or email addressed personally to the potential subject).
    - **3.2.1.** Physical approach: Potential subject may be approached by the investigator if one of two conditions applies:
        - **3.2.1.1.** The investigator has an existing clinical relationship with the patient. In contrast to section 2.1.1 above, the patient must be aware of this existing relationship; that is, the patient must already know the investigator in his clinical role; or
        - **3.2.1.2.** Someone with an existing clinical relationship has approached the patient, introduced the existence of the research study in question, and asked permission for the investigator (or her representative) to approach the subject to discuss the research.
          Other personnel who may have access as described above (investigator with existing clinical relationship but who has never met the potential subject, or persons who have other professional access to identifiable information) may not directly approach the potential subject without introduction by a care provider and the express permission of the subject. Under limited circumstances, the IRB may approve approach by such persons without prior introduction.
    - **3.2.2.** Verbal Contact
        - **3.2.2.1.** Verbal contact initiated as a result of identification through existing clinical relationship will follow the same pattern as for physical approach described in 2.1.1 above.
        - **3.2.2.2.** Verbal contact initiated based on the Conditions of Treatment Form designation ("opt-in" designation) must follow procedures described in HRPP policy 3.6 (Subject Recruitment Through Direct Invitation) (which specifies the content and format of communication and frequency and timing of messages.
    - **3.2.3.** Written contact: Written contact must follow procedures described in HRPP policy 3.6 (Subject Recruitment Through Direct Invitation) (which specifies the content and format of communication, identification of recipient and sender, return contact information, and frequency and timing of messages).

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## 4.0 Ethical Access for Review of Medical Records

- **4.1.** For research that involves review of existing or prospective records, and where consent of the subject has been waived under HHS or FDA regulations, the requirement for ethical access will still apply to identification of potential subjects, as per section 3.1 above.

## 5.0 IRB Procedure

- **5.1.** Investigators must describe how they have ethical access in the subject identification and recruitment section of the IRB application, or the appropriate section of the Medical Records Application.
- **5.2.** The IRB (or the expedited reviewer) will evaluate ethical access as part of its determination whether or not the research satisfies the criteria for approval (45 CFR 46.111(a)(7); "When appropriate, there are adequate provisions to protect the privacy of subjects …")
- **5.3.** If the investigator does not have ethical access for the purposes of recruitment, the investigator may consider adding a co-investigator with the appropriate access, whose role would be to introduce the potential subject to the investigator (as per section 3.2.1.2).
- **5.4.** If the investigator wishes to use a research coordinator acting on her behalf, the IRB or expedited reviewer, or IRB Chair or Executive Chair will determine whether ethical access can be extended to include that coordinator as per section 3.1.1.1.1.
- **5.5.** If the investigator does not have ethical access for the purposes of review of medical records, the investigator may consider adding a co-investigator with the appropriate access, whose role would be to identify potential subjects and gather de-identified data for the investigator. This role can also be taken by an "honest broker" (per HRPP policy 3.4; Use of Protected Health Information in Research)
- **5.6.** Review of medical records must also satisfy requirements of the HIPAA Privacy Rule per HRPP policy 3.4 (Use of Protected Health Information in Research).

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# 3.13 Use of Placebo or Wash-Out of Effective Therapy in Clinical Trials

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for IRB review and approval of clinical trials that utilize placebos or wash-out of effective therapy.

## 2.0 Policy

- **2.1.** It is the policy of the Organization that use of placebo in a controlled clinical trial, or of a wash-out period from effective therapy, must be ethically and scientifically justified, and risks associated with placebo or wash-out must be minimized.
- **2.2.** It is the policy of the Organization that subjects be adequately informed of the use of placebo or of wash-out of effective therapy, and of the associated risks.

## 3.0 Definition

- **3.1.** Placebo is an inactive substance or treatment that may resemble an active medication or treatment, but has no therapeutic value.
  The OHRP Institutional Review Board Guidebook Glossary defines placebo as "a chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug."
  - **3.1.1.** This policy refers use of a placebo in a RCT where the placebo is used as an alternative to the clinical intervention being tested (that is, intervention X vs placebo). The use of placebo when subject is also receiving the standard care (for example, standard treatment + intervention X vs standard treatment + placebo) generally does not pose an ethical concern in and of itself.
- **3.2.** Randomization is assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically.
  The OHRP Institutional Review Board Guidebook Glossary notes that "Random assignment of subjects to conditions is an essential element of experimental research because it makes it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention."
- **3.3.** Wash-Out Period refers to a protocol required period of withdrawal from current treatment prior to initiation of placebo or active treatment arms. "Wash-out" of effective therapy prior to institution of "investigational therapy" in a clinical trial may be ethically problematic, especially if the clinical trial includes a placebo arm.

## 4.0 Ethical Justification

- **4.1.** The use of a placebo as an alternative to "standard therapy" may be ethically justified in the following situations:
  - **4.1.1.** There is no standard therapy.
  - **4.1.2.** Standard therapy is known to be not effective (that is, standard therapy is no better than no treatment).
  - **4.1.3.** Standard therapy may be effective, but associated with significant toxicity such that there is doubt regarding the net therapeutic advantage of the standard treatment.
  - **4.1.4.** Standard treatment is unavailable.
  - **4.1.5.** There are compelling and scientifically sound methodological reasons the use of

placebo is necessary AND the patients who receive placebo will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention (WMA Declaration of Helsinki (2013)).

- **4.2.** The use of a "wash-out" of effective therapy may be ethically justified when there are compelling and scientifically sound methodological reasons for the wash-out AND subjects will not be placed at additional risks of serious or irreversible harm during the wash-out period (or during the duration of the trial if subsequently assigned to placebo).

## 5.0 Study Design Considerations

- **5.1.** The investigator must demonstrate, and the IRB must find that:
  - **5.1.1.** The risk of placebo or of wash-out of effective therapy is minimized. Procedures to minimize risk may include, but are not limited to:
    - **5.1.1.1.** Careful and frequent monitoring for worsening of underlying condition
    - **5.1.1.2.** Early withdrawal of subjects for worsening of underlying condition, or for non-improvement
    - **5.1.1.3.** Early intervention or treatment (including, when appropriate, resumption of known effective therapy)
    - **5.1.1.4.** Exclusion of patients at increased risk of harm from wash-out, or non-response associated with placebo
    - **5.1.1.5.** Cross-over study design, where all subjects receive investigational treatment or intervention at some point in the study
    - **5.1.1.6.** Interim monitoring by DSMB
  - **5.1.2.** Possible assignment to the active study drug offers the prospect of at least equivalent direct subject benefit compared to standard treatment.

## 6.0 Informed Consent Requirements

- **6.1.** For clinical trials utilizing placebo, the informed consent process and document must include:
  - **6.1.1.** A statement that a placebo is used in the study and an appropriate lay definition of "placebo" (for example "a pill or injection that has no medicine in it").
  - **6.1.2.** The scientific rationale for use of a placebo, in lay terms.
  - **6.1.3.** The risks of non-treatment associated with placebo, including worsening of the subject's disease or condition.
  - **6.1.4.** The plan for early withdrawal from the study if the subject's clinical status worsens or fails to improve to a pre-defined level.
- **6.2.** For clinical trials utilizing wash-out of effective therapy, the informed consent process and document must include:
  - **6.2.1.** A statement that the research will utilize a wash-out period where subject will be taken off therapy that has been effective.
  - **6.2.2.** The scientific rationale for the wash-out period, in lay terms.
  - **6.2.3.** The risks of the wash-out period, including worsening of the subject's disease or condition by discontinuing effective therapy.
  - **6.2.4.** The plan for early termination of the wash-out and resumption of effective therapy if the subject's clinical status worsens.

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# 3.14 Phase I and First-in-Human Studies

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for IRB review and approval of Phase I and First in Human Studies.

## 2.0 Policy

- **2.1.** It is the policy of the Organization that, except in limited circumstances, phase I studies are assumed to represent no direct benefit to subjects/
- **2.2.** It is the policy of the Organization that review of phase I studies requires a careful assessment of the risk-benefit relations, subject selection, study design, monitoring and the process and content of informed consent.

## 3.0 Definitions

- **3.1.** ***Phase I studies*** represents the initial administration of an investigational new drug into humans, or into a specific population of humans (for example, elderly subjects, or children). The primary aim of a phase I study is determination of safety and tolerability, and assessment of maximum tolerated dose (MTD). Phase I studies may also assess pharmacokinetics, pharmacodynamics, drug metabolism, structure-activity relationships, and mechanism of action of the investigational agent. Participants in phase I trials may suffer from a disease or condition which could be the eventual target of the investigational agent (for example, an anti-neoplastic drug in patients with advanced cancer), or they may be healthy volunteers. In the former instance, early measurement of drug activity may be a secondary objective. Participants in phase I drug tests may receive a completely novel agent, an agent belonging to a class of drugs already studied in humans or a combination of new and approved drugs
- **3.2.** ***First-in-Human (FIH)*** trials represent the subset of phase I studies where the investigational agent has not been previously used in humans. The starting dose for a FIH phase I trial is typically based on the No Observed Adverse Effect Level (NOAEL), the highest dose at which no statistically significant and/or biologically relevant adverse effect is observed in the most relevant animal species.
- **3.3.** ***Phase 0 studies*** (also referred to as pre-phase I studies) are conducted prior to phase I trials to determine whether further human trials are worth pursuing. Objectives and endpoints of phase 0 studies conducted under an exploratory IND may include evaluating modulation of a presumed drug target in humans; optimizing target assay methodology using human samples; providing pharmacokinetic (PK) data; assessing PK/pharmacodynamics (PD) relationships; and selecting the most promising agent from several chemical entities or formulations. Study participants, who can be either patients or healthy volunteers, are administered sub-therapeutic but pharmacologically active doses of drug. Participant exposure to the agent is limited. Phase 0 studies have no therapeutic intent.

## 4.0 General Principles

- **4.1.** Phase 0 studies have no potential for direct benefit.
- **4.2.** Phase I studies of new agents alone generally are considered to have no potential for direct benefit. Assertions of potential benefit must be based on clear pre-clinical data, or preliminary clinical data in a different population of subjects, at the dose levels proposed in the research.
- **4.3.** Phase I studies of a new agent in combination with an agent with known effectiveness, administered to subjects with a disease or condition, may be considered to have potential for direct benefit.

- **4.4.** Phase I studies of approved agents administered to new specific population of subjects (for example, elderly subjects, or children) with a disease or condition, may be considered to have potential for direct benefit.

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## 5.0 IRB Review

- **5.1.** As a part of the analysis of the ethical basis for the research and the regulatory criteria for approval, the IRB should consider the following points
  - **5.1.1.** ***Assessment of risk***
    - **5.1.1.1.** In most cases, risk assessment is based on pre-clinical data, and can be difficult. Pre-clinical data may fail to predict human risks, leading to adverse effects in human trials (for example, consider the TGN1412 trial). It may predict clinical benefits that then fail to materialize for human subjects. And it may predict nonexistent risks in humans with the result that a potentially useful agent is discarded (Dresser J. J Law Med Ethics 37:38, 2009)
    - **5.1.1.2.** When phase I trials involve healthy people, there should be stronger preclinical evidence that risks are low than there need be when trials involve people with an underlying serious disease.
  - **5.1.2.** ***Assessment of potential benefit***
    - **5.1.2.1.** Potential direct subject benefit should be considered as noted above (section 4.0)
    - **5.1.2.2.** Potential benefit to an individual subject is usually conceptualized in the form of an improvement in health status derived from the agent being tested; however this is not always the sole potential therapeutic benefit. For example an improvement in the quality of life may qualify as a clinically relevant benefit (Chapman AR. J Clinic Res Bioeth 2:113, 2011).
    - **5.1.2.3.** Extraneous benefits such as payment or adjunctive medical services that might benefit individual participants should not be considered when conducting a risk-benefit analysis (Emanuel EJ, et al. JAMA 283: 2705, 2000)
  - **5.1.3.** ***Subject Selection***
    - **5.1.3.1.** Choice of subject population (healthy volunteers vs patients with a disease or condition) should depend on the scientific objectives of the trial, as well as the risks associated with the intervention and the consequences of those harms should they occur.
    - **5.1.3.2.** If patients with a disease or condition are considered the appropriate subjects, careful consideration should be given to the choice of “stable well-managed patients” vs those with poor managed, debilitating or end-stage disease. The former group may be more likely to benefit, may provide better data, and may be likely to make a free and deliberate choice. However the consequences of harm arising from participation may be greater than for those for whom there are limited other choices, or for whom death or disability is inevitable.
    - **5.1.3.3.** When healthy volunteers are considered as appropriate subjects, care must be taken to assure payment (if offered) does not constitute undue inducement and is not exploitative, and that potential subjects do not conceal personal information that could disqualify them from trial enrollment in order to receive payment.
  - **5.1.4.** ***Study design and toxicity monitoring***
    - **5.1.4.1.** Trials should be designed with sequential, rather than concurrent, enrollment. There must be an adequate interval for monitoring effect of the agent on a subject before the next subject is enrolled, and before a dose escalation is made.
    - **5.1.4.2.** The data and safety monitoring plan should be sufficiently robust to assure that subjects are not exposed unnecessarily to harm. The plan should include frequent and clear safety evaluations, well defined dose limiting toxicities, and adequate oversight.
  - **5.1.5.** ***Informed consent***
    - **5.1.5.1.** Extreme care must be taken to avoid therapeutic misconception and unrealistic optimism.
      - **5.1.5.1.1.** “Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce

generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial." (Henderson GE. PLoS Med 4(11):e324, 2007). Two core concepts are (1) subjects need to understand that the main purpose of the research protocol is to produce generalizable knowledge; and (2) conducting a research protocol differs from providing individualized care (Pentz RD. Cancer 118(18):4571, 2012).

- **5.1.5.1.2.** Unrealistic optimism "occurs when people perceive their own personal outcomes as being more positive than those of other people in similar circumstances when, in fact, there is no good reason to do so." Unrealistic optimism may compromise autonomous decision making when it interferes with the appreciation and processing of information related to risks and benefits (Crites JS. J Med Ethics 39(6):403, 2013)

- **5.1.5.2.** General concepts and specific language for ICFs are described in section 6.0 below

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## 6.0 Informed Consent Model Language

- **6.1.** Methods
  - **6.1.1.** For Phase I studies conducted in classic 3 + 3 design, or similar dose escalation design, CF language should reflect the escalation of dose (between cohorts) to toxicity. For example: "The purpose of the study is to find the highest dose of X that can be given safely. To do this a small number of subjects are given a low dose of X, and side effects are noted. If the side effects are tolerable, then the next group will get a higher dose, and this will be repeated with successive groups until some patients get certain side effects. The particular dose you get will depend on when you enter the study. The dose you get will not increase."
- **6.2.** Risks
  - **6.2.1.** For Phase I studies conducted in classic 3 + 3 design, or similar dose escalation design, CF language should reflect the escalation of dose, with development of worse or new adverse effects in higher dose cohorts For example: "The dose of X will be increased with each successive group of subjects in order to see what dose causes side effects. Therefore, depending on when you enter the study (which group you are in) you may get more side effects, or new side effects, not seen with lower doses."
- **6.3.** Potential Benefits to the Subject:
  - **6.3.1.** CF language should reflect General Principles above (section 4.0).
  - **6.3.2.** When there is potential for direct benefit, it should reflect the disease stage of the target population. For example, while use of a new agent in combination with an agent with an approved chemotherapy regimen may have potential for direct benefit, such benefit is unlikely to be significant or long-lasting in a patient with late stage cancer.
  - **6.3.3.** When potential benefits are suggested, the CF language should highlight differences between the study definition of positive response and the way that patients would define it.
    *For example, a phase I oncology trial CF should alert subjects to the fact that tumor response is not equivalent to clinical improvement.*
    *For example: "It is possible that X [the investigational agent] would make your tumor shrink. However, it is important to understand that the tumor shrinking might not mean you will live longer, or even that your symptoms will improve"*
  - **6.3.4.** When potential benefits arise from combination of an effective therapy with the investigational agent, CF language should clearly state that the benefit arises from the approved effective agent (which may be available outside the study) unless there is pre-clinical data to suggest the investigational agent augments the efficacy of the approved drug.
    *For example: "It is possible that the combination of [standard therapy] with X [the investigational agent] would make your tumor shrink. However, it is important to understand that the [standard therapy] might cause your tumor to shrink even if you didn't get X."*
  - **6.3.5.** CF language should minimize description of collateral benefit (for example, avoid phrases like "satisfaction associated with helping find a cure for X")

    - **6.3.6.** CF language can include such benefits as improvement in quality of life, or relief of pain, if such benefits are realistic at the lowest dose levels to be administered.
- **6.4.** Potential Benefits to Others
    - **6.4.1.** CF language should describe realistic potential scientific benefits associated with the research, and should avoid framing benefits in terms of FDA approval.
      *For example "The research may help us determine the safest dose of investigational drug X" is acceptable, as opposed to "This research will help develop a new treatment for disease" or "… provide information to allow FDA approval of drug X"*

## 7.0 Phase I Studies in Children

- **7.1.** Use of early phase investigational agents in children may pose ethical challenges. Investigators need to be especially alert to the risks of unreasonable optimism and therapeutic misconception on behalf of the parents who are asked to provide consent (permission). When older children are involved, investigators must pay close attention to eliciting assent and respecting dissent.
- **7.2.** In general, phase I studies in children hold out greater potential for direct benefit, since there is usually already data from adults suggesting efficacy, and starting dose in pediatric trials is usually close to the adult MTD, thereby suggesting less likelihood of a sub-therapeutic dose (Berg SL. Oncologist 12:1336, 2007). Therefore, pediatric phase I trials may potentially be approvable under 21 CFR 50.52 (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects) and 45 CFR 46.405.

## 8.0 Phase I Studies in Decisionally Impaired Persons

- **8.1.** Use of early phase investigational agents in decisionally impaired persons may pose ethical challenges, to the extent that these potential subjects may not be able to provide consent for themselves. Investigators must actively assess capacity to provide consent and assent, especially when capacity may wax and wane. Investigators must structure the consent/assent process in a fashion that maximizes the ability of the prospective subject to provide his/her voluntary, informed agreement to participate.
- **8.2.** Phase I studies in decisionally impaired persons may be more problematic than those conducted in children (section 7.2 above), since there may not be preliminary efficacy data and starting doses may be at the NOAEL (see section 3.2 above). Therefore, there may be no or limited potential direct benefit.
- **8.3.** Criteria for inclusion of decisionally impaired persons, based on risk-benefit relationship, are described in HRPP policy 4.6 (IRB Review of Research Involving Subjects with Impaired Decision-Making Capacity), sections 7.2 (Category 2 – Greater than minimal risk with the prospect of direct benefit) and 7.3 (Category 3 - Greater than minimal risk with no prospect of direct benefit).
  *Note that the latter category requires that the research represent only a minor increase over minimal risk, which is unlikely to be true when conducting research with a novel agent.*

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# 3.15 Managing Radiographic Incidental Findings in Human Subjects Research

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for disclosure, or nondisclosure, of radiographic incidental findings that may affect the management of a subject's current or future health or welfare.

## 2.0 Policy

- **2.1.** It is the policy of the Organization that all human subject research must include provisions for management of unexpected incidental findings.
- **2.2.** This policy applies to radiographs (including but not limited to MRI, fMRI, CT scan, ultrasound, nuclear medicine scans, PET scans, and plain radiographs) that are performed solely for research purposes, when there is not a formal radiologist's report generated and saved in the medical record. This includes research scans performed as a screening procedure to determine whether a potential subject meets eligibility requirements for inclusion, or as a baseline evaluation prior to beginning the research intervention.

## 3.0 Definitions

- **3.1.** ***Incidental Finding (IF)*** is a finding concerning an individual research participant that has potential health implications and is discovered in the course of conducting research but is beyond the aims of the study.

## 4.0 Procedures

- **4.1.** Plan for Review and Disclosure of IFs to Subjects
  - **4.1.1.** The PI has an obligation to handle IFs responsibly and promptly. The time frame of the initial communication with the subject should be consistent with the suspected severity of the finding and the net benefit of the disclosure.
  - **4.1.2.** Prior to commencing the research, the PI must have a plan to validate any IF and confirm its importance for the health and wellbeing of the subject. If the researcher does not have the expertise to make this assessment, he/she must identify an individual who does have this competence. The plan and time course of the review must take into account the type and resolution of scans or tests performed (e.g., anatomic imaging more urgent than functional imaging), and the age and health status (and likelihood of an abnormality) of the subject population.
  - **4.1.3.** During the process of consent, the PI must explain the potential for discovering IFs, describe the steps researchers will follow to evaluate IFs, (including consultation with a qualified clinician), describe what types IFs the PI intends to disclose or withhold, describe the process of disclosure, and inform the prospective subject of their right to refuse to receive information regarding incidental findings
  - **4.1.4.** The PI has a responsibility for ensuring subjects are well informed regarding the potential risks and benefits of disclosure of incidental findings.
- **4.2.** When to Disclose IF Results
  - **4.2.1.** Whether IFs are disclosed to subjects will depend on the investigator's (and, if necessary, the consultant's) assessment of the "net benefit of disclosure."
    - **4.2.1.1.** ***Category A (Strong net benefit):*** (1) information revealing a condition likely to be life-threatening; or (2) information revealing a serious condition that can be

avoided or ameliorated. Category A IFs must be disclosed, unless the subject explicitly refuses to receive the information.
    - **4.2.1.2.** ***Category B (Possible Net Benefit):*** (1) information revealing a nonfatal condition that is likely to be serious but that cannot be avoided or ameliorated, when a research participant is likely to deem that information important. Category B IFs may be disclosed, at the discretion of the investigator, unless the subject explicitly refuses to receive the information.
    - **4.2.1.3.** ***Category C (Unlikely Net Benefit):*** (1) information revealing a condition that is not likely to be of serious health importance; or (2) information whose likely health importance cannot be ascertained. Category C IFs should not be disclosed to subjects.
- **4.3.** Process of Disclosure to Subject
    - **4.3.1.** The time frame of the initial communication with the subject should be consistent with the suspected severity of the finding and the net benefit of the disclosure
    - **4.3.2.** Subjects may refuse to receive information regarding incidental findings. As appropriate, the PI is responsible for explaining to the subject the consequences of non-disclosure.
    - **4.3.3.** Disclosure of IFs should include a medical professional who is knowledgeable about the type of IF found and who is experienced in communicating sensitive medical information.
    - **4.3.4.** IFs should be disclosed directly to the research participant. Investigators may offer to disclose to the subject's PCP (in addition to, or in lieu of disclosure to subject), but this decision must be made by the subject.
- **4.4.** All IFs must be reported promptly to the IRB. All Category A IFs must be reported to the IRB as soon as possible. The report must include the plan to disclose the results to the subject (for categories A and B), or a description of how the results were disclosed if expeditious disclosure was warranted (for example, for a life-threatening finding).
- **4.5.** The PI generally has no obligation to affirmatively search for IFs. The goal of research is to seek generalizable knowledge, not to provide health information to individuals. Thus, in the context of imaging studies, the PI is not obligated to perform extra scans or modify scans to provide clinical information.
- **4.6.** IFs in Pediatric and Adolescent Research Participants
    - **4.6.1.** If incidental findings detected in pediatric or adolescent subjects are to be disclosed (per section 4.2 above) disclosure should be made to parent or guardian.
    - **4.6.2.** If the disclosed minor subject has been judged mature enough to provide assent, then then offer of disclosure should also be made to the subject. These subjects may refuse to receive this information.
- **4.7.** IFs in Adult Research Participants without Decisional Capacity
    - **4.7.1.** If incidental findings detected subjects who lack decisional capacity are to be disclosed (per section 4.2 above) disclosure should be made to LAR.
    - **4.7.2.** If the subject has been judged competent enough to provide assent, then offer of disclosure should also be made to the subject. These subjects may refuse to receive this information.

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## 5.0 Model CF Language

- **5.1.** The following information must appear in the consent forms where the determination is made to disclose IF (as indicated in Section 4.2 above):
*"In the course of this research, you will undergo [type of study or studies]. These tests are done for research purposes, and not to look for any specific abnormalities. The scans/tests are not the same as you might get to diagnose a medical condition. However, occasionally, scans/tests will find something unexpected which the research was not looking for. This is called an "incidental finding." Incidental findings may be nothing to worry about, or they may be significant or even life-threatening.*
*If one of the researchers sees something on your test which he/she is concerned about, he/she may review the scan/test with an expert. The expert review will be supplied if needed with no cost to you. If the researcher and/or the expert thinks the finding may be of importance to you the researcher will tell you. You can refuse to get this information. If you agree he/she will also tell*

*your doctor.*
*There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are also risks. These include anxiety over a finding which may not be real or may not require treatment.*
*You and/or your insurance company may be billed for follow-up to the incidental finding to see if the abnormality is real or a medical problem."*

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## 6.0 IRB Review

- **6.1.** Prior to approval of the research, the IRB must review:
  - **6.1.1.** The plan to validate any IF and confirm its importance for the health and well-being of the subject (per 4.1.2 above).
  - **6.1.2.** The criteria for deciding whether an IF will be disclosed to subjects
  - **6.1.3.** The proposed process of disclosure (per 4.3 above), including the qualifications of the persons who will be disclosing information to the subject
- **6.2.** All category A IFs must be reviewed by the full IRB. The IRB will determine whether the IF represents an unanticipated problem involving risk to the subject, whether the risk benefit relationship of the research is still acceptable, whether risks have been minimized, and whether the CF is adequate

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