NELSON MANDELA UNIVERSITY

Standard Operating Procedures
Research Ethics Committee (Human) (REC-H)

- **Monitoring/continuing review**

REC-H Chairperson, Dr Dalray Gradidge
Email: dalray.gradidge@mandela.ac.za
Tel: 041 504 2511

Version 1.4, September 2023

TABLE OF CONTENTS

1 MONITORING/CONTINUING REVIEW

1. Nelson Mandela University researchers (staff and/or students) of currently active studies making use of human participants are required to complete and submit a progress report on an annual basis.
2. Failure to do so may result in the immediate suspension or termination of all data collection activities linked to the study. In the case of currently active studies which require renewal/extension of data collection activities and/or amendments to the study, the relevant form should be completed and accompany the submitted progress report.
3. Researchers are advised to familiarise themselves with the Documentation prior to completing and submitting a progress report for review. Failure to do so might result in a delay in the review and approval of the progress report, thereby impacting on the ability of the study to continue (if applicable).

1.1 POLICY

1. The mandate of the Human Research Ethics Committee is to protect human research participants. Continuing review of ongoing research is one aspect of this commitment. Continuing review must be substantive and meaningful focussing on whether the balance of risks and benefits for a particular study has changed, whether there are unanticipated findings involving risks to participants and/or others, and whether any new information regarding risks and benefits should be provided to participants. Review must occur within one year of the last approval date, unless the Committee determines that review should occur more frequently. The South African Health Products Regulatory Authority (SAHPRA) requires six monthly progress reports for clinical trials under its jurisdiction. Progress reports using the SAHPRA format are acceptable to the Human Research Ethics Committee. Continuing review is additional to the review required for all amendments, serious adverse events and unanticipated problems.
2. For protocols initially reviewed by the full committee, the Committee must decide whether ongoing reviews/approvals require full-committee or expedited review. The Chair or a designee will perform expedited continuing reviews. These are detailed in this standard operating procedure.
3. When conducting continuing review, the Human Research Ethics Committee should start with the working presumption that the research, as previously approved, does satisfy the prescribed criteria. The Committee should focus on whether there is any new information provided by the investigator, or otherwise available to the Committee, that would alter the Committee's prior determinations, particularly with respect to its prior evaluation of the potential benefits or risks to participants. The Committee should also assess whether there is any new information that would necessitate revision of the protocol and/ or the informed consent document.

1.2 PURPOSE

1. The purpose of this policy is to provide guidance on the continuing review process as required by NMU. The policy also clarifies the consequences for an investigator failing to submit an annual progress report.

1.3 PROCEDURES

1. Department of Health Guidelines

a. According to the Department of Health's Research Ethics Guidelines (2015), the Human Research Ethics Committee must monitor the ongoing conduct of approved research. The frequency and type of monitoring should reflect the degree of risk to participants. The Committee must receive, at least annually, reports from principal investigators on the following issues:
   i. Progress to date, or outcome of completed research.
   ii. Information concerning maintenance and security of records.
   iii. Evidence of compliance with the approved protocol.

iv. Evidence of compliance with any conditions of approval.

b. Further, a research ethics committee may conduct random inspections of research sites, data and signed consent forms and records of interventions (with prior consent and knowledge of participants). As a condition of approval of each protocol, researchers must report:
   i. Serious or unexpected adverse effects on participants.
   ii. Proposed changes in the protocol.
   iii. Unforeseen events that might affect continued ethical acceptability of the study.
   iv. If a study is stopped before the expected date of completion and provide reasons.

2. Continuing Review

a. Continuing review is a broad term that covers a range of possible procedures depending on the level of risk inherent in a study. For example, depending on the level of risk, the Human Research Ethics Committee may request:
   i. More frequent, than annual, continuing review.
   ii. Sequential continuing review, for instance after the enrolment of a few participants.
   iii. Independent monitoring of the consent process and rigorous evaluation of participants' understanding of the protocol and of being a research participant.

b. The Human Research Ethics Committee must determine at the time of the initial and at the time of each continuing review whether it is necessary for future continuing reports to be submitted more frequently.
   i. Criteria which may be used to determine whether continuing review should occur more frequently include:
   ii. Magnitude of risks.
   iii. Participants' vulnerability.
   iv. The experience of investigators in conducting research.
   v. The Committee's previous experience with the investigators (e.g., compliance history, previous problems with the investigator obtaining informed consent, or prior complaints from participantsabout the investigator).
   vi. Magnitude of adverse events which may be irreversible, life threatening or disabling (the more so when there are no off-setting direct benefits to participants).
   vii. The type and magnitude of a risk is unknown, for instance in proof-of-concept research involving initial attempts to find out if a laboratory discovery or hypothesis with potential clinical applicability works as expected when used in humans. The risks cannot be fully described until they are tested in humans and may be irreversible.
   viii. Previous experience indicating that the frequency of adverse events is a potential concern.
   ix. There have been non-compliance concerns which warrant more frequent monitoring.
   x. A protocol raises ethical concerns about research design or implementation for which there is no consensus or where available ethical or regulatory guidance is ambiguous or contradictory, for example using placebos in studies when there is a known effective treatment for a condition such as hypertension.
   xi. The projected rate of enrolment.
   xii. Whether the research involves novel interventions.

c. When the Human Research Ethics Committee is concerned about the levels of risk in a study, in addition to specifying a time interval between continuing reviews, it may specify a participant enrolment number as a threshold for determining when continuing review is to occur. For example, at the time of initial review and approval of a high-risk clinical trial, the Committee might require that continuing review occur either in 6 months or after 5 participants has been enrolled, whichever occurs first. The minutes of full committee meetings should clearly document the approval period (continuing review interval).

1.4 DOCUMENTATION FOR CONTINUING REVIEW

1. The principal investigator is responsible for timely submission of a protocol summary and status report on the progress of the research which includes:
    a. Number of participants enrolled.
    b. Number of participants who withdrew.
    c. Number of participants lost to follow-up.
    d. A summary of any complaints about the research since the last Committee review.
    e. A summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last Committee review.
    f. Any relevant multi-centre trial reports.
    g. Any other relevant information, especially about risks associated with the research. (Have risks and benefits been consistent with those originally anticipated?)
    h. Information regarding requests for changes.
    i. Changes in sponsors or funders.
    j. Changes in research personnel.
    k. A copy of the current informed consent documents, including Afrikaans and Xhosa translations if applicable.
    l. Any newly proposed consent documents.
    m. A summary of any unanticipated problems and available information regarding adverse events. In many cases, such a summary could be a brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document and any investigator's brochure.
2. If the Chair or designees has determined that a protocol requires continuing review at a full committee meeting then, two weeks before the convened meeting, all members must receive and review an electronic protocol summary and a status report on the progress of the study, and at least one member must receive the complete protocol. The following materials are sent to the main reviewer:
    a. A summary containing the relevant information required to determine whether the protocol continues to fulfil the criteria for approval.
    b. A status report on the progress of the research, including any changes previously approved by the Committee.
3. When reviewing the informed consent document(s), the Committee must ensure that:
    a. The currently approved or proposed consent document is still accurate and complete; and
    b. Any significant new findings that may relate to the participant's willingness to continue taking part are given to participants.
4. To efficiently accomplish its continuing review workload, the Chair summarises the progress of a study; a typical summary might include the following information:
    a. The research is proceeding according to the Human Research Ethics Committee-approved protocol.
    b. The rate of participant enrolment is as expected.
    c. There have been no unanticipated problems.
    d. The rate and pattern of adverse events are as expected.
    e. No participants have complained about the conduct of the research or withdrawn from the research.
    f. There is no new published or unpublished information that would alter the Committee's prior determinations, particularly with respect to the Committee's evaluation of the potential benefits and risks to participants and the informed consent process.
    g. No changes to the protocol or informed consent documents are needed.
5. In the absence of the Chair raising any concern about the research, the Committee should be able to complete its continuing review deliberations for such a project within a brief period of time.

6. On the other hand, the following continuing review of a randomised control trial is likely to raise concerns which need more lengthy deliberation:
    a. The rate of serious adverse events occurring in participants is significantly higher than expected.
    b. A completed research project recently reported in the literature identified previously unrecognised risks for the same experimental intervention being tested in the clinical study undergoing continuing review.
    c. The investigator is proposing several substantive revisions to the protocol in response to the new risk information, including the addition of new exclusion and new safety monitoring procedures for participants.
    d. The investigator is proposing substantive changes to the informed consent document which include a description of the new information regarding reasonably foreseeable risks.
7. In these circumstances, the Human Research Ethics Committee needs to spend significantly more time carefully reassessing whether the risks to participants are sufficiently minimised and reasonable, given the new information presented and informed consent document proposed by the investigator, or whether additional changes should be required.
8. The protocol must be approved by a majority of the core (or alternative) members present. After the meeting the investigator is notified in writing of the action taken. Written notification will include the signed annual progress report form The Committee's conditions, if any, must be met before continuing approval may be granted.
9. When approving research with conditions at the time of continuing review, the Committee must specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions.
10. Expedited review of annual progress reports by the Chair or designee follows the substantive approach outlined above.
11. As a rule, initial approval for a research study is for one-year only, with approval expiring on the one- year anniversary date of the original approval date. The continuing review date is set according to the date on which final approval is granted, either by full-committee or expedited review. [Note: this does not apply to US federally-funded or supported research – see below for separate guidance.]
12. Principal investigators are responsible for ensuring that annual progress reports are submitted with enough time for continuing review to take place before the expiry date of the study. The Human Research Ethics Committee does not have the resources to notify investigators when their studies require annual renewal. If an annual progress report is not submitted prior to the expiry date, a study's approval will lapse, and no data may be collected or used during the period of lapsed approval. Where no applications for renewal are forthcoming, a study may be closed.
13. If the full committee (or Chair or designee) does not approve the continuation of a study, it must inform the principal investigator in writing, with reasons for its decision. The principal investigator is invited to respond in person or in writing providing justification for revising the decision or a proposal to change the protocol. The fact that an appeal by the principal investigator is on-going does not change the expiry date of prior approval or the consequences of a lapse in such approval. If the principal investigator appeals the decision the Committee must ensure there is a fair hearing of the appeal.
14. No Human Research Ethics Committee member may undertake or participate in a continuing review of a study in which he/ she has a conflict of interest, except to provide information requested by the Committee.

1.5 Setting the Continuing Review Due Date

1. Note: The US Office for Human Research Protections (OHRP) provides a detailed explanation for determining the effective date of initial IRB approval and the date for continuing review in its Guidance on IRB Continuing Review of Research, November 10, 2010, pp. 30-47:

'*Except when an expedited review procedure is used, the protocol continuing review date is set according to the date of approval by a full committee meeting. Of note, IRB review of an amendment to a research project during the period for which approval is authorised does not constitute continuingreview of the project as a whole, and thus does not extend the date by which continuing review must occur (e.g. beyond one year from the effective date of the initial approval or the most recent continuingreview approval). In order for the research to be approved by the IRB at a convened meeting, it must receive the approval of a majority of the core (or alternative) members present at the meeting (45 CFR46.108(b)). (Put simply, review of amendments does not alter the date by which continuing review must occur because continuing review examines the full protocol, not simply a change to it.)*'

2. Determining the first continuing review date for research reviewed by the Committee at a convened meeting at the time of initial review and approved for one year
3. When the Committee reviews and approves research without conditions at a full committee meeting
    a. When the Committee conducts the initial review of a research project at a convened meeting and approves the research for one year without requiring either (a) changes to the protocol or informed consent document(s), (b) submission of clarifications or additional documents, the effective date of the initial approval is the date of that Committee meeting. In such circumstances, the expiry date of the initial approval period and the date by which the first continuing review must occur may be as late as one year after the Committee meeting at which the research project was initially approved (See OHRP Guidance for an example, p. 41).
4. When the Committee reviews and approves research with conditions at a full committee meeting without requiring further review at a subsequent convened meeting
    a. A much more common scenario is when the Committee conducting the initial review of a research project at a convened meeting takes the following set of actions:
        i. Approves the project for one year
        ii. As a condition of approval, requires (a) changes to the protocol or informed consent document(s), or (b) submission of confirmations of specific assumptions or understandings on the part of the Committee or additional documents, and
        iii. Directs that the Committee Chairperson (or other individual(s) designated by the Committee) to review and determine on behalf of the Committee whether the changes, clarifications, and/ or additional documents to be submitted by the investigator(s) are satisfactory.
    b. Under this scenario, further review by the Committee at a subsequent convened meeting is not necessary for the initial approval to become effective, and the effective date of the initial approval is the date on which the Committee Chairperson (or other individual(s) designated by the Committee) has reviewed and accepted as satisfactory all changes to the protocol or informed consent documents, or any other responsive materials, required by the Committee from the investigator. In such circumstances, the expiry date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after that effective date of initial Committee approval. The OHRP notes that the first continuing review in these circumstances may occur earlier; for example, for logistical reasons the Committee may choose to set the expiry date of the initial approval period at one year from the date of the Committee meeting at which the research project was initially approved with conditions.
    c. The Committee records must include documentation of the date when the Committee Chairperson (or other individual(s) designated by the Committee) determined that all conditions of Committee approval have been satisfied and the approval becomes effective, and the expiry date of the initial Committee approval.

5. Determining the date for the second and all subsequent continuing reviews for research reviewed by the Committee at convened meetings and approved for one-year intervals, including how to maintain a fixed anniversary date for the expiry of annual Committee approvals
    a. The Committee must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Given this requirement, it is important to recognise that the use of the 'effective date' of Committee approval (i.e. the date on which the Committee Chairperson or other individual(s) designated by the Committee has determined that the conditions of approval have been satisfied) – as opposed to the date of the convened meeting at which the Committee approved a research study with conditions – to determine the latest permissible date for continuing review only applies to the first continuing review. For all subsequent continuing reviews of a research study, since there will be an ongoing approved study, the date of the convened meeting when the Committee conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.
6. Anniversary dates for approvals
    a. Given the logistical advantages of keeping the expiry date of the Committee approval period constant from year to year through-out the life of a project, when (a) the Committee grants approval for one year at the time of each continuing review, and (b) the Committee performs continuing review and re-approves (with or without conditions) the research within 30 days before the Committee approval period expires, the Committee retains the anniversary of the expiry date of the initial approval as the expiry date of each subsequent one-year approval period. For example, if the Committee conducts the initial review of a research study and approves it without conditions on October 1, 2022 for one year, the Committee may conduct its first continuing review anytime between September 1 and October 31 2023, and re-approve the research for another one-year period that expires on October 1, 2024. The same timing can be applied to each subsequent continuing review until the research activities involving human participants are completed. (See OHRP Guidance for examples, p. 42-45).
    b. Ultimate responsibility rests with the principal investigator to monitor and track approval periods and to ensure continuing reports are filed in time for Human Research Ethics Committee review, in particular where review by the full committee is needed.
    c. If an investigator fails to provide continuing review information to the Human Research Ethics Committee or the committee has not reviewed and approved a study by the specified continuing review date, the research must stop, unless the committee finds that it is in the best interests of individual participants to continue taking part in the research interventions or interactions. Enrolment of new participants, participant follow-up and data collection may not occur after a study has expired. When continuing review of a study does not occur prior to the end of the approval period specified by the Committee, the Committee's approval expires automatically. Depending on its administrative capacity, the Human Research Ethics Committee will send a letter informing the principal investigator of the suspension but the responsibility rests with the researcher to suspend enrolment.
    d. The determination regarding whether it is in the best interests of already enrolled participants to continue to participate in the research after Committee approval has expired may be made initially by the investigator, possibly in consultation with the participants' treating physicians (if the investigator is not the treating participants' physician, but the investigator as soon as possible must submit a request for confirmation that the Committee agrees with the determination. The determination by the Committee may be made by the Committee Chairperson, by another Committee member or group of Committee members designated by the Committee Chairperson, or at a convened meeting of the Committee Furthermore, this determination maybe made for all enrolled participants as a group or for each individual participant. If the investigator or Committee determines that it is not in the best interests of already enrolled participants to continue to

participate, investigators must stop all human participants research activities, including intervening or interacting with participants and obtaining or analysing identifiable private information about human participants.

e. When Committee approval of an ongoing research project lapses and the Committee subsequently re-approves the project, the Committee may approve the project for one year and establish a new anniversary date for the expiry date of subsequent approval periods, or it may re-approve the project for a period of less than one year so as to retain the original anniversary date on which prior approval periods expired.

f. When continuing review of a research project does not occur prior to the end of the approval period specified by the Committee, Committee approval expires automatically. The OHRP does not consider such an expiry of Committee approval to be a suspension or termination of Committee approval. Therefore, such expiries of Committee approval do not need to be reported to the OHRP as suspensions or terminations of Committee approval under the Common Rule.

g. However, if the Committee notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the Committee itself is frequently not meeting the review dates), the Committee should determine whether such a pattern represents serious or continuing noncompliance that needs to be reported to appropriate institutional officials, the Health and Human Services Agency that supported the research, and the OHRP (45 CFR 46.46.103(b)(5).

h. Additionally, researchers who allow a lapse of an annual renewal or who fail to respond to feedback regarding a proposed amendment or adverse or unanticipated event, may be informed that their funding has been frozen, that other proposals will not be reviewed, or that they have triggered a higher level of continuing review, such as an internal audit process.

1.6 Communicating the Human Research Ethics Committee's Continuing Review Determination to Investigators and the Institution

1. The Committee must notify the investigator and the institution in writing of its decision to approve or disapprove proposed research or of modifications required to secure Committee approval of the research. If the Committee decides to disapprove the research, it must include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. The OHRP recommends that the Committee notifies any sponsor or co-ordinating centre of a study (possibly through the investigator) of any decision to disapprove the research and the reasons for its decision.
2. The REC-H's written notification of approval must state:
   a. The period of time for which the project is approved
   b. Any conditions of the IRB's approval
   c. The date by which the next continuing review must occur.
   d. Written notification includes the return of the signed Annual Progress Report Form.

1.7 Suspension or Termination of HREC Approval of Research or Disapproval of Research at the Time of Continuing Review

1. The Committee has the authority to suspend or terminate approval of research that is not being conducted in accordance with the Committee's requirements or that is associated with unexpected serious harm to participants (45 CFR 46.113). A suspension or termination of Committee approval of research may occur at any time during the period for which Committee approval has already been given.
2. For a multicentre research project for which many or all institutions engaged in the research project choose to rely on their local Committees' review of the project, a local Committee's decision at one

institution to suspend or terminate its approval of the research only applies to the conduct of the research project at that institution.

3. The Committee must promptly report any termination or suspension to the investigator, appropriate institutional officials, the Health and Human Services (HHS) agency that supported the research and the OHRP (45 CFR 46.103(b)(5) and 46.113). Such reports must include the reasons for the Committee's action (45 CFR 46.113).
4. **Committees must follow written procedures for ensuring such reporting (45 CFR 46.108(a)). When reporting the suspension or termination of Committee approval of a research project to the OHRP, the OHRP recommends that the report include the following information:**
    a. The name of the institution (e.g. university) conducting the research
    b. The title of the research project and the title of any related grant, contract or cooperative agreement
    c. The name of the principal investigator for the research project
    d. The REC-H REF number and the number of HHS award(s) (e.g. grant, contract)
    e. The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged non-compliance, educate the investigator, educate all research staff, and require monitoring of the investigator or the research project).
5. **When the Committee (a) suspends or terminates its approval during the period for which the Committee approval has already been given or (b) disapproves a research project at the time of continuing review, the Committee should establish procedures to ensure the rights and welfare of currently enrolled participants are protected, participants are not put at risk, and participants receive appropriate care, if indicated, during the period of suspension or following the cessation of the research. This is particularly important in the context of clinical trials. For example, the Committee, in consultation with the principal investigator and the participants' physicians, may need to determine whether it is in the best interests of currently enrolled participants to:**
    a. Continue receiving the interventions that were being administered to participants under the research project
    b. Be transferred to another institution engaged in the research so that participants' participation in the research can continue
    c. Be transitioned to medical management outside the research context.
    d. Continuation of participants on interventions that were being administered under the research project may be appropriate at least temporarily, for example, when those interventions hold the prospect of direct benefit to participants or when withholding those interventions poses increased risk to the participants. If the Committee decides that already enrolled participants should continue to receive the interventions administered during the research, data collection (especially safety information) should also continue for such participants.

1.8 Identifying the Point when Continuing Review is No Longer Necessary

1. Continuing review and re-approval of a research project at least annually is required so long as the research involves human participants. The OHRP considers a research project to continue to involve human participants as long as the investigators conducting the research continue to obtain:
    a. Data about the participants through intervention or interaction with them
    b. Identifiable private information about the participants in the research.
2. With respect to obtaining identifiable private information, the OHRP considers this to include obtaining identifiable biological specimens originating from living individuals. This includes:
    a. Collecting or receiving identifiable private information (including identifiable biological specimens) from any source (i.e., not already in the possession of the investigator)
    b. Collecting identifiable private information by observing or recording private behaviour without interacting or intervening with human participants

c. Using, studying or analysing identifiable private information (including identifiable biological specimens), even if the information was already in the investigator's possession before the research begins. This includes using, studying or analysing any of the following:
   i. Identifiable private information obtained by interacting or intervening with human participants
   ii. Identifiable private information stored in documents, records, photographs, images, video recording or audio recordings provided to the investigators from any source
   iii. Identifiable private information stored in documents, records, photographs, images, video recording or audio recordings already in the investigator's possession before the research begins
   iv. Identifiable private information obtained about an individual by interviewing other people
   v. Identifiable biological specimens provided to the investigators from any source
   vi. Identifiable biological specimens already in the investigator's possession before the research begins

3. A research project no longer involves human participants once the investigators have finished obtaining data through interaction or intervention with human participants or obtaining identifiable private information about the participants, which includes using, studying or analysing identifiable private information. Once all such activities described in the Committee-approved protocol are finished, the project no longer needs to undergo continuing review. For example, when the only remaining activity of a research project involves the analysis of aggregate data sets without individual participant identifiers, no further continuing review is necessary. At that point, the Committee can formally close its file for the project and advise the investigator of that action. Similarly, maintaining individually identifiable private information without using, studying or analysing such information is not human participants' research and thus does not require continuing review.

1.9 Study Closure or Final Report

1. A study is considered active or ongoing until a study closure or final report is submitted to the Human Research Ethics Committee. This is also consistent with FDA regulations (21 CFR 56.108) which require prompt reporting to the Committee of any changes in research activity, and completing a study is considered a change in activity.
2. The principal investigator can voluntarily close a study when completed and Human Research Ethics Committee approval is no longer required, when all participant accrual is completed and/or all data (including study follow-up data) pertaining to participants have been collected and when no further interaction with participants is planned for research purposes. In multi-centre commercial trials, the principal investigator must provide confirmation from the sponsor that all participants have completed their final visits and follow-up at the local site (i.e. Mandela University) is complete.
3. To formally close a study, the principal investigator must submit a final report specific to that study. Final reports will be reviewed and approved by an expedited process. The principal investigator will be sent written notification of the study's closure, including a signed original copy of the Final Closure Report. If a study is not closed but is allowed to expire as a lapse in approval, an administrative suspension letter may be sent to the principal investigator.
4. If a principal investigator terminates employment with the University, he or she must submit a final report to the Human Research Ethics Committee or transfer the protocol to another principal investigator via an amendment which requires Committee approval. If the principal investigator is unwilling or unable to provide such an amendment, the Committee may choose to administratively close the study.

1.10 VERIFICATION OF NO MATERIAL CHANGES SINCE PRIOR HUMAN RESEARCH ETHICS COMMITTEE REVIEW

1. The Human Research Ethics Committee or other agents designated by the Committee may determine at any point during the period of approval for a particular protocol that the protocol requires verification from sources other than the investigator that no material changes have occurred since prior Committee review.
2. The nature of the study will determine from which source verification is to be requested. The decision will be made on a case-by-case basis using, among others, the following sources of verification:
    a. Pharmacy distribution records
    b. Data Safety Monitoring Boards
    c. Sponsors
    d. Research participants' records
    e. Hospital medical records
3. A request for verification that no material changes have occurred since prior Human Research Ethics Committee review may be made by, among others:
    a. The Human Research Ethics Committee based on information in the continuing review form.
    b. The Chair, a Committee member, the Committee's administrative staff.
    c. An investigative subcommittee or an independent audit team.
4. Examples of criteria which might alert the Human Research Ethics Committee to the need for such verification include:
    a. Randomly selected projects.
    b. A potential incident of non-compliance raises concern.
    c. Complex projects conducted by investigators who previously have failed to comply with research ethics guidelines or determinations of the Committee.
    d. Projects where concerns about possible material changes occurring without Committee approval have been raised based on information in the continuing review reports or from other sources.