Section 4: GETTING STARTED IN THE SUBMISSION PROCESS

4.1. Other Committee Reviews

This is a brief overview of some of the other committees that may need to review a human subject protocol.

Scientific or Scholarly Evaluation required prior to IRB review may include:

A. Departmental Review Committee (*UIC OPRS Review Only*): Written evaluations of the merit, acceptability and feasibility of the study design and procedures, risks and benefits (*refer to UIC OPRS form Appendix F: United/Departmental Review Committee for Research Involving Human Subjects)* from two faculty or staff appointed by the head of the investigator's Department/Unit accompany protocols submitted for initial convened IRB review. (*UIC campus requirement for collaborative studies only when protocols are reviewed by OPRS).*

B. Faculty Advisor or Department Head: The Faculty Advisor (*for student submissions*) or Department Head confirms by signing the initial and continuing review applications that the research meets the standards of the discipline. This "signature" can be provided "electronically" on IRBNet.

C. UIC Cancer Center-PRC: When appropriate, scientific and feasibility review (*refer to UIC Cancer Center for more information*) of cancer-related protocols are performed by the CC-PRC prior to initial IRB review for research not previously peer-reviewed by NCI and simultaneously with initial IRB review for NCI peer reviewed protocols. Continuing review of cancer-related protocols by the CC-PRC occurs at the same time as IRB continuing review. Written copies of the CC-PRC reviews are provided to the IRB (*Applies to UIC collaborative studies only at this time. For more information please contact OPRS*).

D. UIC Clinical Research Center-SAC: When appropriate, scientific and feasibility review (*refer to UIC RSS form Appendix G : CRC Application)* by the CRC-SAC occurs for all proposals requesting use of the CRC as a performance site. For protocols requesting use of the CRC, approval from the CRC-SAC is required prior to IRB initial review approval or approval of an amendment reflecting the involvement of the CRC in the research. Written copies of the CRC-SAC reviews are provided to the IRB.

   The UIC Clinical Research Center (CRC) reviews research to be performed at the UIC Clinical Research Center. The CRC performs a scientific, feasibility and utilization assessment of all new clinical studies. The UIC CRC review replaces the Departmental Review (*Appendix F*) in the initial protocol submission process, when submitting studies to OPRS on the main campus.

   NOTE: *Final IRB approval of new protocols will not be released until documentation of CRC review has been received.*

   I. Initial Protocol Review (For Submission Using the CRC Only).

   A. Investigators submit their proposed research studies to the CRC prior to submission of the IRB application to RSS for IRB review.

   B. Investigators include the CRC approval letter or documentation of conditional CRC approval with their protocol application to the IRB.

C. RSS staff screens the initial protocol applications to determine whether the study involves the use of the Clinical Research Center and is subject to the CRC review. If so, RSS staff ensures that the application includes the appropriate CRC approval letter.

D. Although a protocol application may be scheduled for review prior to CRC approval, final IRB approval will not be issued without final CRC approval. RSS staff will ensure that the investigator has submitted this documentation before issuing IRB approval.

E. RSS provides the CRC a copy of the IRB approval notice.

II. Continuing Protocol Review.

A. For CRC research studies, in addition to the IRB, investigators must submit a continuing review to the CRC. The CRC review cycle is based upon the approval period (*no less than once a year)* established by the IRB.

B. The investigator submits the CRC Continuing Review Form to the CRC in parallel to submission of the Continuing Review application to the IRB. In contrast to initial review, CRC approval is not required for the issuance of Continuing IRB approval.

C. Following the issuance of continuing review approval, copies of the approval notices are exchanged between CRC and RSS, and retained in the respective file.

III. Other Submissions (*amendments, final reports, complaints, protocol violations, unanticipated problems and other events requiring prompt reporting, and non-compliance findings*).

A. The RSS handles the submission (*amendments, final reports, complaints, major protocol violations, unanticipated problems and other events requiring prompt reporting, and allegations of non-compliance*) in accordance with the respective COM-R HSPP policies and procedures.

B. For CRC research studies, following IRB review of the submission, the RSS sends the CRC a copy of the correspondence sent to the investigator.

IV. Institutional Reporting.

A. In accordance with UIC HSPP policy Reporting of Unanticipated Problems, Suspensions, Terminations, and Non-Compliance, for CRC research studies, the CRC also receives a copy of the report sent to institutional officials, supporting agency heads, and regulatory agencies, including but not limited to:

1. Unanticipated problems and other events requiring prompt reporting;
2. Continuing and/or serious non-compliance;
3. IRB suspension; and/or
4. IRB termination.

V. Quality Assurance / Improvement Findings.

A. If the OVCR Quality Improvement Program (QIP) conducts a directed or routine Quality Improvement audit of a CRC protocol, the OVCR Associate Director for Research Compliance will disseminate a copy of the final report to the CRC.

B. If the CRC conducts an audit or inspection of an IRB approved study, a copy of the final report will be provided to the OVCR Associate Director for Research Compliance. The OVCR Associate Director for Research Compliance forwards the report to the IRB and/or RSS in accordance with UIC HSPP policy and procedures.

E. Institutional Biosafety Committee (IBC): Any protocol using rDNA or infectious agents must first be submitted to the IBC and approved before final IRB approval can be granted. Forms and application instructions are available on the COM-R IBC webpage.

F. Radiation Safety Committee (RSC): This committee authorizes the use of radiation-producing devices and radioactive material in operations, education, research, and development activities. The RSC establishes radiation policies and procedures for the University in accordance with state and federal regulatory requirements governing the procurement, use, storage, and disposal of radiation-producing devices and radioactive material. The RSC authorizes individual investigators and study personnel to use these devices in the conduct of their research; however, prospective users must submit proposals to the RSC for review and approval. The RSC review is completed prior to initial review conducted by the IRB, which may not approve research requiring RSC review without prior approval from the RSC. Forms and application instructions are available on the RSC webpage. For more information contact the Biomed Department at 815-395-5680.

The UIC Environmental Health & Safety Office (EHSO) has a policy *(Radiation Safety: Human Subject Research Protocols)* adopted by COM-R that defines when research protocols involving human subjects require review by the EHSO/COM-R RSC prior to IRB review and approval. **NOTE:** Contact the Director of the COM-R Physical Plant for any questions concerning laboratory inspection or Environmental Health & Safety issues on the Rockford campus. The telephone number is 815-395-5834.

Protocols requiring review by UIC EHSO/COM-R RSC include:

1. Research protocols involving radiation exposure for research purposes and that involve increased exposure for the subject versus standard of care due to additional procedures or more frequent procedures;

2. Research protocols that require review by the RDRC as they involve the use of a radioactive labeled drug as defined by the FDA;

3. Protocols involving greater than 100 mrem exposure per year and having an estimated effective equivalent dose below 25 rem per year whole body, 250 rem per year individual organs and tissues, and 75 rem per year eyes. These protocols require RSO review. These effective equivalent doses are for patient research subjects only. The Radiation Safety

Committee will not approve an effective equivalent dose greater than 5 rem per year to any healthy human research subject;

4. Research protocols with an estimated effective equivalent dose above 25 rem per year whole body, above 250 rem per year individual organs and tissues or 75 rem per year eyes; and
5. Protocols involving the use of investigational medical devices emitting ionizing radiation (*i.e., not having FDA approval*).
6. The EHSO/COM-R RSC provides the IRB with a risk assessment and a determination regarding the research prior to IRB review and approval to ensure that the IRB has the information required in order to make the necessary determinations as required by the approval criteria outlined in the regulations [*45 CFR 46.111(a)(1)(2), 21 CFR 56.111(a)(1)(2), 38 CFR 16.111 (a)(1)(2)*].

   (1) Risks to subjects are minimized:
   - (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
   - (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purpose.

   (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

7. For protocols requiring EHSO/COM-R RSC review, approval notification from EHSO/COM-R RSC must be received prior to IRB review and approval. Typically, this approval should be obtained before IRB submission. If it is not, IRB review will not proceed until this is obtained.

I. Initial Review:

A. The investigator provides the research protocol and consent document, IRB application form, and any additional supporting documents required to the UIC EHSO/COM-R RSC for radiation safety review before submission to the IRB.

B. The submission is reviewed by the appropriate committee (*i.e., UIC EHSO, COM-R RSC*).

C. When it has been determined that radiation use is appropriate and safe and the consent document language adequately represents the radiation risks, a letter of determination, noting the full title of the research and the PI, is provided to the PI and copied to the RSS Office. Based upon these letters, RSS will maintain a log of all approved initial review submissions. The RSS will also maintain a log of correspondence from the EHSO/COM-R RSC whereby it was determined the radiation use/exposure was not acceptable in the proposed research.

D. The EHSO/COM-R RSC approval letter should be included in the initial submission application to RSS. If not included, the RSS file copy may be used to supplement the investigator's application, but the PI will be notified of the omission for subsequent submissions.

E. The approval letter to the PI will note that additional review by the EHSO/COM-R RSC is required for any amendments that affect the radiation exposure and also for the CR application. PIs must allow for the additional time required for this safety review.

F. EHSO/COM-R RSC is copied on the IRB approval letter, as applicable.

II. Amendment Review:

A. If a change is made to the research that involves an increase in radiation dose or a change in body exposure site, the amendment must be reviewed by the EHSO/COM-R RSC to evaluate the risks to subjects. The amendment may not be submitted to the IRB until the EHSO/COM-R RSC has reviewed the revisions to the research and/or consent document.

B. A letter of determination is provided to the PI and copied to the RSS Director. RSS will maintain a log of all amendments that have received EHSO/COM-R RSC approval.

C. Once the PI receives the EHSO/COM-R RSC review notification, the PI can then submit the amendment application for IRB review. IRB approval cannot be provided without EHSO/COM-R RSC review documentation included in the application materials. If not included, the RSS file copy may be used to supplement the investigator's application, but the PI will be notified of the omission for subsequent submissions.

D. EHSO/COM-R RSC is copied on the amendment approval letter, as applicable.

III. Continuing Review:

A. Investigators must submit all applicable IRB submission materials and materials required by the EHSO/COM-R RSC policy for Continuing Review well in advance of the expiration of the approval of the research protocol (*allow an additional time for EHSO/COM-R RSC review*).

B. EHSO/COM-R RSC reviews the safety information provided in the Continuing Review application to ensure that no additional risks related to radiation exposurehave been identified in the past approval period. If any revisions are required to the research based upon the EHSO/COM-R RSC review, the investigator is notified by EHSO/COM-R RSC in writing that an amendment is required and the RSS Specialist for the IRB is copied on the determination letter. If changes are not required, the investigator is notified in writing that the CR is cleared to submit for IRB review and approval. The RSS Specialist is to be copied on this communication. RSS will maintain a log regarding EHSO/COM-R RSC Continuing Review approvals and requests for revisions.

C. If the Continuing Review is IRB approved, the EHSO/COM-R RSC is copied on the approval letter, as applicable.

IV. Protocol Deviations:

EHSO/COM-R RSC policy requires that "any deviation in participant radiation dose administration from the approved protocol must be reported in writing immediately to the RSO." According to COM-R HSPP policy this would be an unanticipated problem that would require prompt reporting to the IRB using the *Event Requiring Prompt Reporting to the*

Institutional Review Board form. If the RSS/IRB receives a report of an event that meets the reporting requirements within the EHSO/COM-R RSC policy, the EHSO/COM-R RSC will be notified promptly and will be copied regarding any IRB determinations.

References:
21 CFR 56.111(a)(1)(2)
38 CFR 16.111(a)(1)(2)
45 CFR 46.111(a)(1)(2)

G. Radioactive Drug Review Committee (RDRC): Applies to UIC collaborative studies only at this time. For more information please contact OPRS.

H. Data Safety Monitoring Board (DSMB) / Data and Safety Monitoring Plan (DSMP): (*NIH funded protocols for clinical trials*) A data safety monitoring plan is a general plan contained in the research protocol to ensure the safety of the subjects and to ensure the validity of the data. The essential elements of a data and safety monitoring plan are:

- Monitoring the progress of trial and the safety of participants;
- A description of the mechanism for reporting unanticipated problems involving risks to subjects or others (UPIRSOs), as well as adverse events (AEs), to the IRB, FDA, sponsor, and NIH, if applicable; and
- Plans for assuring data accuracy and protocol compliance.

Data Safety Monitoring Board / Data Monitoring Committee:

A Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a group of individuals with pertinent scientific expertise that:

- Reviews, on a regular basis, the accumulated research data from an ongoing clinical trial;
- Advises the sponsor and/or researcher regarding the continuing safety of trial subjects and those yet to be recruited into the research trial; and
- Advises as to the continuing validity and scientific merit of the trial.

(*The terms DSMB and DMC are synonymous and can be used interchangeably*)

Requirements of DSMP and DSMB/DMC:

Not all research protocols require a DSMP or a DSMB/DMC. Every NIH funded investigator conducting a clinical trial, however, should incorporate into the research protocol the following:

- Elements of a data and safety monitoring plan to ensure subject safety (*i.e. safety monitoring and periodic assessments for safety*);
- Methods for reporting UPIRSOs; and
- Measures to protect the confidentiality of the research data (*i.e., privacy, coding, and storage*).

As research protocols become more complicated and the level of risk to subjects increases, the investigator and the IRB have to evaluate the need for a DSMP and/or a DSMB/DMC. The regulations require that, in order to approve the research, the IRB must determine if the research plan makes adequate provisions for monitoring the data collected to ensure the safety of participants [*45 CFR 46.11(s)(6), 21 CFR 56.111(a)(6), 38 DFR 16(a)(6)*]. When appropriate, data and safety monitoring plans can be required for research in any discipline, including social and behavioral research.

NOTE: All research protocols conducted at the Clinical Research Center (CRC) are required to have a DSMP. For additional information regarding the requirements for conducting research at the CRC refer to the CRC website or RSS Appendix G.

When the National Institutes of Health require DSMPs and DSMBs:
In general, the National Institutes of Health (NIH) believe that every clinical trial should have an IRB approved data and safety monitoring plan. The variety and type of monitoring plan may differ depending upon the nature, size, and complexity of the clinical trial being conducted.

A data and safety monitoring plan is required for all types of clinical trials, including physiologic, toxicity, and dose finding studies (*Phase I);* efficacy and safety studies (*Phase II*); and efficacy, effectiveness and comparative trials (*Phase III*).

The size and complexity of the monitoring committee or plan is also adjusted based upon the size or scope of the research. The monitoring may be conducted by the Principle Investigator or the NIH program staff for a small Phase I study while a large Phase III clinical trial may require the establishment of an independent data and safety monitoring Board. However, even trials that pose little likelihood of harm should consider an external monitoring body.

The National Institute of Health (NIH) requires the establishment of data safety monitoring boards for multi-site clinical trials involving interventions that entail potential risks to participants (*generally Phase III clinical trials*). For earlier phase trials (*Phase I and Phase II*), a DSMB may be appropriate if the studies involve multiple clinical sites, the studies are blinded or masked, or the studies involve high-risk interventions or vulnerable populations. A DSMB determines that the study is being conducted safely and effectively, and recommends early closure if significant risks have developed or if new information indicates that the trial is unlikely to be completed successfully.

Whatever the plan, IRBs should be provided feedback on a regular basis, usually at the time of continuing review. The feedback should include a summary of UPIRSOs, a summary of adverse events as required by NIH policy, and a copy of the DSMBs reports with any recommendations regarding the research. At a minimum, all monitoring plans must include a description of the reporting mechanisms for reporting adverse events to the IRB, the FDA, and the NIH. The investigator must ensure that the NIH is informed of any actions the IRB may take as a result of continuing review of the research.

Individual institutes within the NIH have their own policies regarding data and safety monitoring plans and data and safety monitoring boards, for example National Heart, Lung, and Blood Institute (NHLBI) revised their policy in May of 2005.

Food and Drug Administration (FDA) and DMC for clinical trials:

Current Food and Drug Administration (FDA) regulations do not require the use of data monitoring committees (DMC) in clinical trials except for research studies conducted in emergency settings in which the informed consent requirement is excepted [*21 CFR 50.24(a)(7)(iv)*]. Research of this type is currently not allowed at COM-R under UIC policy.

The FDA believes that all clinical trials require safety monitoring (*i.e. sponsor monitoring, medical monitors, adverse event reporting*), but that not all trials require monitoring by a formal committee that is external to the trial organizers, sponsors, and investigators. DMCs are generally recommended for controlled clinical trials of any size that will compare rates of mortality or major morbidity, but a DMC is not required or recommended for most clinical trials. Additionally, DMCs are not generally needed for clinical trials that address lesser outcomes such as relief of symptoms, unless the clinical trial populations are at elevated risks of more severe outcomes.

DMCs are not usually required in early Phase I and Phase II studies or pilot/feasibility studies, but formal monitoring groups may be appropriate for some early clinical studies, particularly if the risk level is higher than normal or the treatment approach is novel. These monitoring groups may be internal to the sponsor or consist of the investigators. Additionally, if the investigator is the manufacturer or the IND or IDE sponsor who presents the potential for financial or personal conflicts of interest, a DMC with independent members may provide added credibility to the oversight of subjectsafety and validity of the data.

IRB Duties Concerning DMC Required Studies:

COM-R IRB members determine that research plans include provisions for monitoring the data to provide adequate protections for the safety of subjects. The COM-R IRB members articulate when provisions for data and safety monitoring are required. The IRB members use the appropriate review guide as a reference to determine when data and safety monitoring is necessary. For additional information, refer to the COM-R Tip Sheet – *Data and Safety Monitoring Plans (DSMPs), Data and Safety Monitoring Boards (DSMBs), and Data Monitoring Committees (DMCs).*

The PI is responsible for accurately providing sufficient information in the appropriate application so that the IRB members have sufficient information to make a determination as to whether the protection provisions for monitoring data to ensure the subjects' safety is appropriate.

References:

NIH Policy: Policy for Data and Safety Monitoring, June 10, 1998
NIH Policy: Further Guidance on a Data and Safety Monitoring For a Phase I and Phase II Trials, June 5, 2000
NHLBI Policy: Policy on Human Subjects Research, Data and Safety Monitoring Plans, National Heart, Lung, and Blood Institute (NHLBI)
FDA Guidance: Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006.

I. Embryonic Stem Cell Research Oversight (ESCRO) Committee:

The University of Illinois, College of Medicine at Rockford Embryonic Stem Cell Research Oversight (ESCRO) committee shall apply standard practices to the review of research activities submitted for

approval. This policy sets forth the initial, continuing review and amendment process to be performed by ESCRO.

I. Introduction:

The COM-R is committed to the ethical and responsible use of human embryonic stem (hES) cells in research. As such, the COM-R's participation in hES cell research will be conducted in accordance with the general principles expressed in the *Guidelines for Human Embryonic Stem Cell Research (NAS, 2005).*

II. Institutional Delegation of Authority:

The Chancellor of the UIC delegated authority to the COM-R Regional Dean (IO) to establish a committee with oversight responsibility for COM-R institutional hES cell research. The committee shall review all proposed and ongoing hES cell research on the Rockford campus and maintain a registry of all hES cell lines that are imported into or maintained at COM-R. Human embryonic stem cell research shall include all derivations of hES cell lines and all research using hES cells derived from:

A. Human blastocysts made for reproductive purposes and later obtained for research from *in vitro* fertilization (IVF) clinics;

B. Human blastocysts made specifically for research using assisted reproductive technology;

C. Human somatic cell nuclear transfer (NT) into oocytes.

III. Committee Review if the Research is:

A. Conducted by COM-R faculty, staff or students; or

B. Performed on the premises of COM-R; or

C. Using equipment belonging to COM-R; or

D. Using funds administered by COM-R; or

E. Satisfying a requirement imposed by COM-R for the award of a degree or the completion of a course of study; or

F. Conducted by adjunct faculty, including non-salaried faculty, with the intention of citing COM-R affiliation in a publication or study documents.

IV. Establishment and Rules of the Embryonic Stem Cell Research Oversight (ESCRO).

The committee shall be called Embryonic Stem Cell Research Oversight (ESCRO). ESCRO shall have authority to review and approve the following areas of research in which COM-R is engaged:

A. All established hES cell lines listed on the National Institutes of Health (NIH) Human Embryonic Stem Cell Research Registry (http://stemcells.nih.gov/research/registry/);

B. All established hES cell lines that are not currently listed on the NIH Registry; and

C. All new hES cells lines derived from one of the following sources:

1. Human blastocysts made for reproductive purposes and later obtained for research purposes from In vitro fertilization (IVF) clinics, or

2. Human blastocysts made specifically for the purpose of research using assisted reproductive technologies, or

3. Human somatic cell nuclear transfer (NT) into human oocytes for the purpose of creating hES cells.

V. Research Not Permitted to be Undertaken by COM-R Includes:

A. Research involving in vitro culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first;

B. Research to which hES cells are introduced into nonhuman primate blastocysts or in which any embryonic stem cells are introduced into human blastocysts;

C. Research that involves the breeding of any animal into which hES cells have been introduced at any stage of development; or

D. Research that involves human somatic cell NT for the purpose of reproductive cloning.

ESCRO shall advise the Regional Dean (IO) in all matters relating to COM-R use and procurement of hES cells and shall assure that all such research complies with all policies contained within this document.

ESCRO shall develop and provide appropriate training for COM-R investigators on the conduct of research using human embryonic stem cells.

The Regional Dean (IO) is responsible for providing adequate resources to ESCRO to facilitate its charge, including the provision of meeting space, staff support, etc.

The Regional Dean (IO) may not override an ESCRO denial of approval. However, even after ESCRO has approved the research, the IO may require further institutional review and may make the determination that certain types of hES research may not be undertaken at COM-R.

VI. ESCRO Composition:

ESCRO shall consist of scientists with expertise in the areas of stem cell research, developmental biology, molecular biology, and assisted reproduction; and individuals with training/ credentials in the areas of ethics and law. The Committee shall also consist of an individual who is not affiliated with the institution in any way other than as a member of the ESCRO Committee.

VII. Investigator Responsibilities:

A. The investigator in charge of a project that involves hES cells shall prepare and submit to ESCRO such documents as required by ESCRO in conducting its charge.

B. The submission must be approved by ESCRO prior to the investigator's:
   1) Acceptance of funding and
   2) The initiation of the research.

Exception: Research involving only in vitro use of federally approved hES cell lines (*all established hES cell lines listed on the National Institutes of Health (NIH) Human Embryonic Stem Cell Research Registry*) may begin upon registration with ESCRO and

after receiving final approval from other applicable COM-R Committees (*e.g., IBC, IRB, etc.*). Awards for funding may be accepted prior to registration with ESCRO.

C. Significant changes in registered and/or approved research shall be submitted to ESCRO for review and approval prior to implementation.

D. The investigator in charge of the research project will cooperate with ESCRO and the institution and prepare any requested reports.

VIII. ESCRO Approval and Oversight:

A. ESCRO shall have the authority to review and approve, require modifications in (*to secure approval*) or deny approval of all research activities involving hES cells engaged in by COM-R. Initial approval will be for a maximum of one-year and, after review, a research activity may be reapproved for a continued period.

B. In making its determination, ESCRO *WILL* consider the following:

1. Conformity with all applicable state and federal laws, regulations, guidelines and all applicable University policies; and
2. The anticipated risks, benefits and significance of the knowledge to be gained; and
3. The qualifications and training of the investigator and key personnel to conduct the research.

Research activities using hES cells that *REQUIRE* review and approval by *OTHER* COM-R Committees (*e.g., IBC, IRB, etc.*) should be submitted to ESCRO as follows:

IF	THEN
In vitro use of NIH cell lines	Register with ESCRO after obtaining approval of other COM-R committees
In vivo use in animals of NIH cell lines	Submit to ESCRO simultaneously with submissions to other COM-R committees
In vivo use in humans of NIH cell lines	Submit to ESCRO simultaneously with submission to other COM-R committees
All research involving established non-Federally approved hES cell lines	Submit to ESCRO first
All research involving derivation of new hES cell lines	Submit to ESCRO first

No research may be initiated until ALL required approvals are obtained:

4. ESCRO shall conduct continuing review studies at intervals that it deems appropriate. As part of the continuing review, ESCRO may obtain and review materials submitted to other committees (*IBC, IRB, etc.*)

5. ESCRO shall have the authority to observe or have a third party observe the conduct of any research activity subject to ESCRO oversight. ESCRO has the authority to request all records associated with the conduct of the research.

IX. Conflict of Interest:

All Investigators submitting research activities to ESCRO must disclose conflicts of interest in the research proposed. Conflicts of interest are defined in accordance with UIC Conflict of Interest Policy (http://tigger.uic.edu/depts/ovcr/research/conflict/RNUA/policy/index.shtml).

No ESCRO committee member may participate in the review or approval of a research activity in which they have a real or perceived conflict of interest, except to provide information requested by ESCRO. In addition to the UIC Conflict of Interest Policy, conflicts of interest may include a member's association with the research (*e.g., listed investigator, employment in the laboratory of the principal investigator or co-investigator*).

X. Recordkeeping:

ESCRO shall maintain a complete file of each hES cell study including research application, correspondence, etc. ESCRO shall maintain copies of meeting minutes. Minutes shall document attendance, conflict of interest, research reviewed, controverted issues and their resolution, and committee vote. Records shall be retained in accordance with UIC policies and all applicable state and federal laws, regulations, and guidelines.

XI. Non-compliance:

Alleged deviations from the COM-R ESCRO policies should be reported to the ESCRO chair for investigation, resolution and reporting to the Regional Dean (IO) and COM-R committees with shared jurisdiction (*IRB, IBC, etc.*). ESCRO shall have the authority to suspend or terminate its approval of hES cell research that is not being performed in compliance with ESCRO policies, University policies, applicable state or federal laws, regulations, and/or the general principles expressed in the NAS *Guidelines for Human Embryonic Stem Cell Research*.

ESCRO, through the Regional Dean (IO) shall report suspension or termination of research to external funding sources, if applicable. The IO, or designee, has the authority to further review suspected deviations and to suspend or terminate approval of hES cell research.

XII. Additional Policies, Guidelines, Plans and Procedures:

ESCRO may develop policies, guidelines, and/or procedures to execute its charge. Such documents will be made available to the UIC community.

XIII. Levels of Review and Approval:

The Chair or the Chair's designee shall screen submitted protocol applications to determine the level of review.

A. Registration and administrative review:

When the research activities involve only the in vitro use of human embryonic stem (hES) cells listed on the NIH Registry for approved hES cell lines, the protocol application is eligible for administrative review and approval by the Chair or the Chair's designee.

1. Research activities receiving administrative review may be approved by the

reviewer, but may NOT be denied approval by the reviewer. Rather, studies NOT receiving approval must be referred for convened committee review.

2. Continuing review of a study initially approved under this procedure may be conducted in the same manner, unless there have been changes since the initial (*or last*) review that would require designated or convened review.

B. Designated review:

When the research activities involve the in vivo use of hES cells listed on the NIH Registry in animals and the hES cells are not anticipated to make a significant contribution to the behavior or phenotype of the chimeric animal, the protocol application is eligible for designated review to the Committee. The ESCRO members will have five working days in which to determine if review at a convened meeting is required. Any ESCRO member may request that the review be transferred to a convened meeting. When it has been documented that a quorum have received the report, and that no objection has been raised within the prescribed timeframe, a designated review will be assigned by the chair or the chair's designee to review the protocol application.

1. Activities receiving designated review may be approved by the reviewer, but may not be denied approval by the reviewer. Rather, studies not receiving approval must be referred for convened committee review.

2. Continuing review of a study initially approved under this procedure may be conducted in the same manner or if it is determined by the chair that no changes have been made since the initial (*or last*) review that have not been approved, continuing review may be done administratively.

C. Convened committee review:

Submissions that require convened committee review are those which involve any of the following:

1. Any activity eligible for designated review that a member of ESCRO indicates should be reviewed at a convened committee meeting.
2. Any activity that involves the use of an approved hES cell line in vivo in humans.
3. Any activity that involves any use of an established non-federally approved hES cell line.
4. Any activity that involves the development of new hES cell lines, regardless of the method of development.

Submissions meeting any of the criteria above will be assigned a primary and a secondary reviewer by the Chair or the Chair's Designee. However, all ESCRO members will receive copies of the submission for review and consideration in sufficient time prior to the meeting.

Continuing review of a study initially approved under this procedure must be conducted in the same manner if it falls under category C2 through C4 above. Continuing review of studies approved under C1 may, at the discretion of the committee, receive continuing

administrative or designated review. At any point in the process, if questions arise, the ESCRO administrator will contact the investigator before the next stage in the review. At any point in the review or oversight process, ESCRO members may call for a convened committee review of any activity in its entirety.

D. Review Process:

Activities subject to review by the convened committee shall be submitted to the ESCRO administrator by the submission deadline in order to be eligible for review at the next scheduled convened meeting. The ESCRO Chair or chair's designee shall assign a primary and secondary reviewer. The ESCRO administrator shall distribute meeting agendas (*identifying assigned reviewers*) and submissions to the committee members with ample time to allow the committee to review and make any comments.

1. Reviewers shall draft review summaries and notate any concerns to bring to the convened meeting.
2. Convened committee review refers to a convened meeting at which a quorum of the full membership of ESCRO is present. A quorum is defined as a simple majority (*one-half plus 1*) of the membership of the ESCRO. For approval, all protocols require a majority vote of the quorum present.
3. When conducting business in the absence of the Chair or when the Chair has a conflict of interest on an activity under review, another experienced member of the committee will serve as the Chair.
4. Investigators may be invited to appear before the ESCRO to present their protocols or respond to questions.
5. The following decisions can be made during the process of convened review:
   a) Approval,
   b) Modifications required. Approved pending minor clarifications/modifications eligible for administrative review and approval,
   c) Deferred for further review at a convened meeting (*Substantive issues must be addressed by the convened ESCRO committee*), and
   d) Denial.

NOTE: *Clarifications/modifications include additions, deletions or corrections that may be required at any step in the review process. If an exact page-for-page exchange is not possible, then all pages affected must be resubmitted. To assist the committee in their review, clarifications and/or modifications should be highlighted in a manner that separates them from the original submission (e.g., bolded, underlined, highlighted, etc.).*

6. Meeting minutes will be maintained that document attendance and summarize the controverter issues, their resolution and the vote (*for, against, abstained*).
7. The determinations of the committee will be conveyed to the investigator in writing in a timely manner by the ESCRO administrator. Reasons for denial will likewise be documented and conveyed to the investigator in writing.

E. Activities eligible for designated review:

Following submission, the Committee members will have five working days to determine if a protocol should be reviewed at a convened meeting. Any member may request that a review be done at a convened meeting. Following determination that a quorum of the committee have received the report, and that no member has requested review at a convened meeting, the chair or the chair's designee will assign a reviewer.

1. Reviewers shall provide review summaries and concerns to the ESCRO administrator.
2. Determinations of the reviewer will be conveyed to the investigator in writing in a timely manner by the ESCRO administrator.
3. Revised protocol applications shall be submitted to the ESCRO administrator who will forward the revisions to the reviewer for review.
4. Reviewers shall provide further concerns to the ESCRO administrator or approval within seven working days of receipt of the revisions.
5. Approval of the protocol will be conveyed to the investigator in writing in a timely manner by the ESCRO administrator.
6. The ESCRO administrator shall regularly prepare a report of all protocols reviewed and approved by designated review and present the report to the committee for acknowledgement as the next convened meeting.

F. Activities eligible for administrative review:

The Chair or the Chair's designee will assign a reviewer promptly after submission.

1. Reviewers shall provide review summaries and concerns to the ESCRO administrator within seven working days of being assigned as a reviewer and receiving protocol.
2. Determinations of the reviewer will be conveyed to the investigator in writing in a timely manner by the ESCRO administrator.
3. Revised protocol applications shall be submitted to the ESCRO administrator and the office will forward the revisions to the reviewer for review.
4. Reviewers shall provide further concerns to the ESCRO administrator or approval within seven working days of receipt of the revisions.
5. Approval of the protocol will be conveyed to the investigator in writing in a timely manner by the ESCRO administrator.
6. The ESCRO administrator shall regularly prepare a report of all protocols reviewed and approved by administrative review and present the report to the committee for acknowledgement at the next convened meeting.

G. Timeliness:

In order to avoid unnecessary delays in the initiation of research activities, the review process should be accomplished within 30 days of the timely receipt of a properly completed protocol application. At any stage of the review process, if an investigator does

not submit requested clarifications/modifications within 60 days of notification, the submission review may be terminated and the file closed. If clarifications/modifications cannot be submitted within 60 days of notification, the investigator should contact the ESCRO administrator to request an extension of response time.

H. **Appeals:**
Appeals of ESCRO decisions should be directed to the chair. While an approval by ESCRO may be subject to additional institutional review and may be subsequently denied, a denial by ESCRO may not be overturned by another institutional body or official.

I. **Approval, re-approval, and amendments:**
Initial approval of ESCRO will be for a maximum of one year from the date of review by the convened committee, or the designated or administrative review, but may be granted for less than one year at the discretion of the committee.

Approval may be continued upon re-approval of the activity by ESCRO after receipt and review of an activity update report (*continuing review form*). To support the continuation of approval process, the ESCRO administrator will send each investigator a notice of expiration and a request for updates, including an inquiry as to whether any unapproved changes have been made or any additional risks identified. The ESCRO chair or designee shall review requests for re-approval to determine if the request should receive administrative, designated, or convened committee review.

Substantive changes in the research activity will require prospective review and approval by ESCRO before they are implemented. The investigator will submit a request for amendment that outlines the proposed changes and a revised application (*with changes identified*), which will be subjected to the required review process (*see section II above*).

Note: *The expiration date will not be altered by any subsequent amendments.*

4.2. IRB Submission Process

NOTE: All submissions to the COM-R IRB are received by electronic submission. Video and print instructional material can be accessed by going to http://irbnetresources.org/. Click on the word "resources" in the first sentences and then insert the user name "uicomr" and password "training" to access the instructional material. It is very important to only use one IRB Net ID number for a protocol throughout all subsequent submissions to provide easy tracking for reviewers and auditors. Technical assistance is also available by contacting the RSS office at (815) 395-5942.

4.3. Independent Decision Concerning Research Activity

In order to insure compliance with the COM-R FWA the COM-R policy requires that **NO researcher can make an independent decision concerning whether their research activity involving human subjects require IRB review**. Details below provide oversight and instruction on the type of review and the appropriate steps that are needed before any research activity can begin.

4.4. Determining Whether a Performance Site or an Institution is Engaged or Not Engaged in

Research

This section details the rules concerning what research activities should be brought to the attention of the COM-R IRB for review, depending on the location of the activity and/or the association of the researcher.

A. It is the policy of the COM-R IRB to assure that the appropriate approvals and/or written agreements are completed when human subject research involves non-COM-R performance sites.

B. RSS and the COM-R IRB ensures that the appropriate approvals and/or written agreements are completed when human subjects research involves domestic non-COM-R performance sites. (*Refer to COM-R HSPP policy and procedure COM-R IRB "Review of Domestic Research Involving Non-COM-R Sites, Agencies, Organizations, or Institutions"*)

C. RSS, the COM-R IRB, COM-R faculty, staff, students, and COM-R authorized affiliates are required to comply with the terms of the COM-R FWA regardless of the geographic location of the research or the research being conducted.

D. COM-R employees or agents, including faculty, staff, and students, who intend to conduct activities that may in part represent research with human subjects as outlined in this policy and procedure are not authorized to determine independently that the project is subject to the HSPP, except in limited circumstances as a preliminary suggestion. COM-R employee or agent refers to individuals who:
   1) "act on behalf of COM-R;
   2) exercise institutional authority or responsibility; or
   3) perform institutionally designated activities."

   COM-R employees or agents can include staff and students among others, regardless of whether the individual is receiving compensation.

E. If COM-R is not engaged as part of adjunct faculty research, COM-R IRB approval is not required. However, if adjunct faculty wish to use their COM-R credentials in publications they need prior COM-R IRB approval for this research activity.

4.4.1. Rules of Engagement:

A non-COM-R site will be determined by the COM-R IRB to be *ENGAGED* in research when employees or agents of the site:

A. Intervene or interact with living individuals for research purposes; or

B. Obtain individually identifiable information from living individuals for research purposes; and/or

C. The site receives direct federal funding for research purposes.

4.4.2. Rules on Non-Engagement:

A non-COM-R site will be determined by the COM-R IRB to be *NOT* engaged in research when:

A. No research funding will be received by the non-COM-R site;

B. No employees or agents at the non-COM-R site actively participate in the research including, but not limited to, consenting subjects, interacting or intervening with

subjects, and/or collecting and transferring individually identifiable information regarding subjects to the COM-R PI;

C. No other relationship with COM-R, the COM-R PI and key research personnel, and/or agreements with COM-R or the sponsor, indicate that the non-COM-R site is engaged in research activities.

The COM-R HSPP follows the *OHRP Guidance on Engagement of Institutions in Human Subjects Research*, dated October 16, 2008, which is provided word for word in this procedure section. Institutions are considered engaged in an HHS-conducted or supported non-exempt human subjects research project – and, therefore, would need to hold or obtain OHRP-approved FWAs and certify IRB review and approval to HHS when the involvement of their employees or agents in that project includes any of the following (*refer to OHRP Guidance on Engagement of Institutions in Human Subjects Research, dated October 16, 2008, for specific examples*):

A. Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (*i.e., awardees' institutions*), even where all activities involving human subjects are carried out by employees or agents of another institution.

B. Institutions whose employees or agents intervene for research purposes with any human subject of the research by performing invasive or noninvasive procedures.

C. Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment.

D. Institutions whose employees or agents interact for research purposes with any human subject of the research.

E. Institutions whose employees or agents obtain the informed consent of human subjects for the research.

F. Institutions whose employees or agents obtain for research purposes identifiable private information or identifiable biological specimens form any source for the research. It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects research are considered engaged in the research, even if the institution's employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:

1) Observing or recording private behavior;

2) Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and

3) Using, studying, or analyzing for research purposes, identifiable private information or identifiable specimens already in the possession of the investigators. In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

G. Institutions would be considered not engaged in an HHS-conducted or supported non-exempt human subjects research project, and therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS – if the involvement of their employees or agents in that project is limited to one or more of the following. The following are scenarios describing the type of institutional involvement that would make an institution not engaged in human subjects research; there may be additional such scenarios.

1) Institutions whose employees or agents perform commercial or other services for investigators provided that all of the following conditions also are met:
   a) The services performed do not merit professional recognition or publication privileges;
   b) The services performed are typically performed by those institutions for non-research purposes; and
   c) The institution's employees or agents do not administer any study intervention being tested or evaluated under the protocol. (*Refer to OHRP Guidance on Engagement of Institutions in Human Subjects Research, dated October 16. 2008, for specific examples*).

2) Institutions (*including private practices*) not selected as a research site whose employees or agents provide clinical trial-related medical services that are dictated by the protocol and would typically be performed as part of routine clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial investigators provided that ALL of the following conditions also are met:
   a) The institution's employees are agents that do not administer the study interventions being tested or evaluated under the protocol; **and**
   b) The clinical trial-related medical services are typically provided by the institution for clinical purposes; **and**
   c) The institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; **and**
   d) When appropriate, investigators from an institution engaged in the research retain responsibility for:
      (1) Overseeing protocol-related activities; **and**
      (2) Ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.

3) Institutions (*including private practices*) not initially selected as a research site whose employees or agents administer the study interventions being tested or evaluated under the protocol limited to a one-time or short-term basis provided

that all of the following conditions are met:

a) An investigator from an institution engaged in the research determines that it would be in the subject's best interest to receive the study interventions being tested or evaluated under the protocol;

b) The institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research;

c) Investigators from the institution engaged in the research retain responsibility for:

(1) Overseeing protocol-related activities;

(2) Ensuring the study interventions are administered in accordance with the IRB-approved protocol; and

(3) Ensuring appropriate arrangements are made for reporting protocol-related data to investigators at the engaged institution; including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol; and

(4) An IRB designated on the engaged institution's FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an institution not selected as a research site.

4) Institutions who employees or agents:

a) Inform prospective subjects about the availability of the research;

b) Provide prospective subjects with information about the research (*which may include a copy of the relevant informed consent document and other IRB approved materials*) but do not obtain subjects' consent for the research or act as representatives of the investigators;

c) Provide prospective subjects with information about contacting investigators for information or enrollment; and/or

d) Seek or obtain the prospective subjects' permission for investigators to contact them.

5) Institutions (*e.g., schools, nursing homes, businesses*) that permit use of their facilities for intervention or interaction with subjects by investigators from another institution.

6) Institutions whose employees or agents release to investigators at another institution identifiable private information or identifiable biological specimens pertaining to the subjects of the research.

7) Institutions whose employees or agents:

a) Obtain coded private information or human biological specimens from another institution involved in the research that retains a link to individually identifying information; and

b) Are unable to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, for example:

(1) The institution's employees or agents and the holder of the key enter enter into an agreement prohibiting the release of the key to those employees or agents under any circumstances;

(2) The releasing institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the institution's employees or agents under any circumstances; or

(3) There are other legal requirements prohibiting the release of the key to the institution's employees or agents.

8) Institutions whose employees or agents access or utilize individually identifiable private information only while visiting an institution that is engaged in the research, provided their research activities are overseen by the IRB of the institution that is engaged in the research.

9) Institutions whose employees or agents access or utilize individually identifiable private information for purposes of study auditing.

10) Institutions whose employees or agents receive identifiable private information for purposes of satisfying USFDA reporting requirements.

11) Institutions whose employees or agents author a paper, journal article, or presentation describing a human subjects research study.

References:
OHRP Guidance on Engagement of Institutions in Human Subjects Research, dated October 16, 2008.

4.5. Levels of IRB Review

New researchers should familiarize themselves with the following information for guidance on what form to use for various research activities.

4.5.1. Administrative Review:

COM-R policy requires that PIs get official administrative review and approval prior to accessing patient medical or billing records or using certain types of data sets in a research activity. PIs MUST fill out the "Determination of Whether an Activity Represents Human Subject Research" form and submit this on IRB Net to receive a formal Administrative Review for any of the following research categories:

1. Public Use databases that have de-identified datasets; **or**
2. A novel case report that is limited to one case study (*two or more requires an elevated level of review*); **or**
3. Your project involves research that is limited to death records, autopsy materials, or cadaver specimens *(provided that the cadaveric tissues/cells are not used for clinical investigations);* **or**

4. Your project is limited to course-related activities designed specifically for educational or teaching purposes; where data is collected from and about human subjects as part of a class exercise or assignment and is not intended for use outside of the classroom *(example: Research Day or public presentation).*

5. Your project is limited to a program evaluation, human factors evaluation, or quality assurance methodologies, where the data will not be shared outside the department that is seeking to evaluate their program or service.

6. You wish to review medical health/billing records to determine if there are sufficient numbers of human subjects to allow a research study to be designed.

NOTE: *Please keep a record of the "Determination" form and the decision letter for your records.*

4.5.2. Claim of Exemptions:

Research in which activities involving human subjects are limited to one or more of the categories at 45 CFR 46.101(b) [38 CFR 16.102(b)] may qualify for exemption from 45 CFR 46.

. PIs do NOT have the authority under federal guidance and COM-R policy to independently determine that research involving human subjects is exempt. PIs must submit the research to RSS for review of a claim of exemption and receive written documentation of the determination from RSS before initiating the research.

A. For research conducted at COM-R and other non-performance sites, the following individuals may review and approve claims of exemption: IRB Chair, IRB member designated by the Chair, RSS Special designated by the Chair.

B. Even though federal regulations do not require a continuing review of an exempt study, COM-R policy does require the PI to submit an annual continuing review application for each claim of exemption and to submit a final report upon the completion of the study.

4.5.2.1. General Considerations in Making a Determination of a Claim for Exemption:

A. The research involves no more than minimal risk to participants.

B. The research cannot involve prisoners as participants. (*45 CFR 46.101(i)*).

C. Exemption categories 1-5 *DO NOT* pertain to FDA-regulated research. (*21 CFR 56.104*).

D. Exemption categories 1—6 apply to research involving pregnant women, fetuses and neonates (*45 CFR 46.201(b)*), with the exception that VA Research may not involve the fetus as a subject.

E. Exemption categories 1 and 3-6 apply to research involving children. Research activities in category 2 are exempt for children only when limited to educational tests or observation of public behavior when the investigators do not participate in the activities being observed. (*45 CFR 46.401(b)*).

4.5.2.2. Categories of Research Activities Identified as Exempt by COM-R:

A. **Category 1.** Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

1. Research on regular and special education instructional strategies, or
2. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
[*45 CFR 46.101(b)(1), 38 CFR 16.102(b)(1)*]

B. **Category 2**. Research involving the use of educational tests (*cognitive, diagnostic, aptitude, achievement*), survey procedures, interview procedures or observation of public behavior, unless:

1. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; AND
2. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, loss of insurability (this later criteria is for VA Research only; 1200.05) or reputation.
[*45 CFR 46.101(b)(2), 38 CFR 16.102(b)(2)*].
3. If the research in this category involves children as participants, the activities cannot include (*45 CFR 46.401(b)*):
    a) Survey procedures;
    b) Interview procedures;
    c) Observation of public behavior where the investigators participate in the activities being observed.
4. Additional guidance.
    a) This category requires that information is recorded in a manner that:
        (1) Participants cannot be identified, directly or through their responses, demographics, or codes linked to identifiers, or
        (2) If participants can be identified, directly or through their responses, demographics, or codes linked to identifiers, any disclosure of the participants' responses outside the research could not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability or reputation.

C. **Category 3.** Research involving the use of educational tests (*cognitive, diagnostic, aptitude, achievement*), survey procedures, interview procedures, or observation of public behavior that is not exempt under category 2 above, if:

1. The human subjects are elected or appointed public officials or candidates for public office; or
2. Federal statute(s) require(s) without exception that the confidentiality of

the personally identifiable information will be maintained throughout the research and thereafter. [*45 CFR 46.101(b)(3), 38 CFR 16.102(b)(3)*].

D. **Category 4.** Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, provided:

1. These sources are publicly available, or
2. The information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. [*45 CFR 46.101(b)(4), 38 CFR 16.102(b)(4)*]
3. Additional guidance:
   a) Publicly available means that the general public can obtain the date/biological specimens. Sources are not considered publicly available if access to the data/specimens is limited to researchers.
   b) All material that will be used to conduct the research must exist at the time the research is proposed; no on-going or prospective collection of material is allowed.
   c) Under this exemption, an investigator may review identifiable records, but must record information in the research record in a non-identifiable manner. Moreover, the data must be permanently and completely de-linked at the time of extraction (*that is, the investigator will not have any further access to the identifiable records*).
   d) Exemption from IRB review does not also represent an exemption from HIPAA requirements for authorization or waiver of authorization when the research involves the use or access of PHI.
   e) Research involving the retrospective analysis of medical records qualifies for exemption category 4 when the information extracted from the chart and recorded in the research record does not contain any identifiers, including most of the 18 HIPAA elements (*dates of service and geographic codes less specific than street address are allowable*), codes derived from any of the HIPAA elements or codes linked to identifiers. The investigator must also receive a waiver of HIPAA authorization from the IRB, as looking at medical records is considered accessing PHI regardless of whether or not identifiers are being recorded.
4. For VA Research, if exemption category 4 is claimed, the investigator may NOT retain any of the 18 identifiers outlined in the HIPAA Privacy Rule, and the investigator may NOT have access to any code by which the information may be linked to individuals. When the investigator will review PHI for the research, a waiver of authorization is required.

5. Research involving the retrospective analysis of medical records does not qualify for a claim of exemption if prospective rather than retrospective data is collected, any of the 18 HIPAA elements, except dates of service and geographic codes less specific than street address, combinations of the elements are entered into the research records, or data contained in the research records are linkable in any way to the identity of the subjects.

E. **Category 5.** Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study, evaluate, or otherwise examine:
   1. Public benefit or service programs;
   2. Procedures for obtaining benefits or services under those programs;
   3. Possible changes in or alternatives to those programs or procedures; or
   4. Possible changes in methods or levels of payments for benefits or services under those programs. [*45 CFR 46.101(b)(5), 38 CFR 16.102(b)(5)*].
   5. Federal guidance specifies that the following criteria must be satisfied to apply this exemption:
      a) The program under study must deliver a public benefit (*e.g., financial or medical benefits as provided under the Social Security Act*) or service (*e.g., social, supportive, or nutritional services are provided under the older Americans Act*);
      b) The research or demonstration project must be conducted pursuant to specific federal statutory authority;
      c) There must be no statutory requirement that the project be reviewed by the IRB; and
      d) The projects must not involve significant physical invasions or intrusions upon the privacy of participants.
      e) Authorization or concurrence of the Federal funding agency for the exemption determination is needed. For VA Research, determination of exempt status for these research and demonstration projects must be made by the Under Secretary of Health on behalf of the Secretary of Veterans Affairs.

F. **Category 6.** Taste and food quality evaluation and consumer acceptance studies, if:
   1. Wholesome foods without additives are consumer; or
   2. A food is consumed that contains a food ingredient at or below the level found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service

of the U.S. Department of Agriculture. [*45 CFR 46.101(b)(6), 38 CFR 16.102(b)(6)*].

4.5.2.3. Exempt Research and Belmont Report:

Although exempt research is not subject to the federal regulations at 45 CFR 46 (*or 38 CFR 16*), the COM-R policy requires all research involving human subjects, including exempt research, to be performed responsibly and in accordance with the ethical guidelines of the Belmont Report. Researchers performing exempt research are expected to institute appropriate protections, including obtaining informed consent as appropriate and implementing measures to protect privacy and confidentiality.

4.5.2.4. Procedure:

Please follow the instructions detailed in the Claim of Exemption form and Claim of Exemption Checklist available on the RSS webpage and IRBNet in the Library Manager section.

The RSS Specialist conducts a pre-submission review after the application package has been submitted on IRBNet. After all requested modifications have been completed the formal Exemption Review is conducted.

A. In making the determination, the reviewer considers whether:

1. The research meets the definition of research involving human subjects;
2. The selection of subjects is equitable;
3. The research involves no more than minimal risk;
4. The research involves prisoners;
5. The research involves children;
6. The research activities fit one or more exemption categories;
7. The research is FDA regulated;
8. The proposed recruitment procedures and consent process are appropriate;
9. The consent process, when applicable, informs participants of the following:
    a) The activity is research;
    b) Name, affiliation, and contact information for the investigator
    c) Purpose of the research;
    d) Description of the procedure;
    e) Participation is voluntary;
    f) Measures to protect the privacy of subjects and the confidentiality of the research data;
    g) Description of any reasonable foreseeable risks as well as anticipated benefits;
    h) Statement that the researcher is available to answer any questions.
10. Adequate provisions exist, when applicable, to protect privacy interests of

subjects and maintain the confidentiality of the data.

B. The reviewer makes one of the following determinations:
   1. Certification of exemption is granted;
   2. Additional information or modifications needed before a final determination can be made;
   3. Proposed activity does not meet the definition of research involving human subjects;
   4. Research proposal does not meet the criteria for exemption and must be reviewed by the IRB under expedited or convened review processes;
   5. For research meeting the criteria for exemption category 4 and involving the retrospective review of medical records, the reviewer determines whether a waiver of HIPAA authorization is warranted.

4.5.2.5. Communications.

A. The investigator is notified of the reviewer's determination by e-mail and a formal posting in IRBNet.
   The communication contains, as applicable:
   1. Any issues requiring resolution;
   2. Recommendations for changes in the level of review;
   3. Requests for further information; and
   4. For research granted an exemption, documentation of:
      a) The exemption category(ies);
      b) The expiration date of the exemption certification;
      c) The investigator's responsibility to submit any modifications to the research to RSS for review and certification prior to implementation;
      d) Review of any informed consent documents, recruitment materials, or research instruments;
      e) If applicable, waiver of HIPAA authorization;
      f) If applicable, Optional Form 310 – Protection of Human Subjects, Assurance Identification/Certification/Declaration.

B. The IRB is notified of protocols granted an exemption by listing them on the agenda for the next IRB meeting. The meeting minutes related to the agenda also list the protocols granted an exemption during that time period.

4.5.2.6. Amendments:

Any proposed amendments to a project that has received a certification of exemption must be submitted to the RSS for review and certification of exemption prior to implementation. The proposed amendment is submitted using the amendment submission form. Amendments to research protocols that were granted an exemption are reviewed to determine whether or not

the change to the research would alter the exempt status, thus requiring either expedited or convened IRB review.

4.5.2.7. Expiration:

It is the policy of the Rockford IRB to require an annual update on studies granted an exemption from IRB review in order to stay current with all research being conducted on the Rockford campus. Claims of Exemption are issued an expiration date of one year.
Investigators are sent reminders at 90, 60, and 30 days before the expiration date.
Investigators must submit a Continuing Review application to continue or a Final Report on IRBNet to close out the study. If no Continuing Review application or Final Report is submitted, the study is closed 30 days after expiration of the IRB approval.

References:

21 CFR 56.104(c)-(d)
38 CFR 16.101(b), 38 CFR 16.301(a), 38 CFR 16.401(b), 38 CFR 16.101(b)(1)-(b)(6)
45 CFR 46 101(b), 45 CFR 46.31(a), 45 CFR 46.401(b)
OHRP Guidance on 45 CFR 46.101(b)(5): Exemption for Research and Demonstration Projects on Public Benefit and Service Programs
OPRR Guidance on Exempt Research and Research that may Undergo Expedited Review, May 5, 1995
OHRP Guidance on the Involvement of Prisoners in Research May 23, 2003
VHA Handbook 1200.05 para.3 and 8, Appendix A

4.5.3. Expedited Reviews:

Expedited review is a process that allows certain types of research protocols (*initial and continuing review*) and changes to protocols (*amendments*) to be reviewed outside of an IRB meeting by one or more experienced IRB members. Expedited review refers to a process and not to the speed at which a protocol or submission is reviewed. Expedited review occurs outside the IRB meeting; therefore, items submitted for expedited review do not need to follow the submission deadlines.

A. Two Basic Criteria For Initial Review:

In order to be eligible for expedited review at **initial review**, a protocol must first meet the criteria for:

1. Minimal Risk, which means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinary encountered in daily life or during the performance of routine physical or psychological examinations or tests (*45 CFR 46.102(i), 21 CFR 56.102(i)*).

2. The research must be limited to the procedures detailed in one or more of the seven initial review expedited review categories.

B. Criteria For Subsequent Reviews:

Once the above two criteria are met, an IRB may use the expedited review procedure to review either or both of the following on subsequent reviews (*continuing review or amendments*):

1. Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk; **AND/OR**

2. Minor changes in previously approved research during the period (*of one year or less for which approval is authorized*). Minor changes means a proposed change in research related activities that does not materially affect an assessment of the risks and benefits of the study **AND** does not substantially change the specific aims or design of the study (*i.e., administrative changes, minor revisions, word for word modifications, etc.*).

4.5.3.1. Expedited Eligibility:

Federal regulations limit the use of expedited review procedures to specific research categories published in the Federal Register *(please see the list below in Section 4.5.3.2.*). (*45 CFR 46.110; 21 CFR 56.110; 38 CFR 16.110*). The categories on the list apply regardless of the age of the participants, except as noted.

4.5.3.2. The Seven Expedited Initial Review Categories:

A. Category 1:

Clinical studies of drugs and medical devices only when condition (a) **or** (b) is met.

(a) Research on drugs for which an investigational new drug application (*21 CFR Part 312*) is not required. ***Note:*** *Research on marketed drugs that significantly increase the risks or decrease the acceptability of the risks associated with the use of the product is not eligible for expedited review.*

(b) Research on medical devices for which:

(i) an investigational device exemption application (*21 CFR Part 812*) is not required; **or**

(ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

B. Category 2:

Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; **or**

(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

C. Category 3:

Prospective collection of biological specimens for research purposes by noninvasive means.

Examples:

(a) hair and nail clippings in a nondisfiguring manner;

(b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

(c) permanent teeth if routine patient care indicates a need for extraction;

(d) excreta and external secretions (*including sweat*);

(e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

(f) placenta removed at delivery;

(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

(h) supra and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

(j) sputum collected after saline mist nebulization.

D. Category 4:

Collection of data through noninvasive procedures (*not involving general anesthesia or sedation*) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/ approved for marketing. (*Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications*.)

Examples:

(a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

(b) weighing or testing sensory acuity;

(c) magnetic resonance imaging;

(d) electrocadiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

(e) moderate exercise, muscular strength testing where appropriate given the age, weight, and health of the individual.

E. Category 5:

Research involving materials (*data, documents, records, or specimens*) that have

been collected, or will be collected solely for nonresearch purposes (*such as medical treatment or diagnosis*).

NOTE: *Some research in this category may be exempt from the HHS regulations for the protection of human subjects. [45 CFR 46.101(b)(4)]. This listing refers only to research that is not exempt.*

F. Catory 6:

Collection of data from voice, video, digital, or image recordings made for research purposes.

G. Category 7:

Research on individual or group characteristics or behavior *(including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior*) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

NOTE: *Some research in this category may be exempt from the HHS regulations for the protection of human subjects, 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.*

IMPORTANT: The activities listed in the expedited review categories are not to be deemed of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. The OHRP decision chart 8 illustrates the determination for expedited review. It is available at:
http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm

4.5.3.3. Designation of Individuals Who May Conduct Expedited Review:

The IRB Chair can designate in an *IRB Member/Staff Delegation of Responsibilities* form an IRB administrator as individuals who are authorized to perform expedited review of minor changes (*administrative changes, minor revisions, word for word modifications, etc.*) of responses to the IRBs requests for modifications to initial applications, continuing review, and amendments that meet the criteria for expedited review.

4.5.3.4. Experience and Qualifications of Expedited Reviewers:

IRB member/staff delegation of responsibilities must:

1. Demonstrated knowledge and ability to consistently apply regulatory requirements, COM-R HSPP policies and procedures, ethical principles, concerning research and the IRB review process; and
2. Sufficient experience as an IRB member or RSS Specialist with demonstrated adherence to research compliance principles.

4.5.3.5. Criteria of IRB Review:

One or more IRB members can review the submission submitted for expedited review

to determine whether it meets the requirements for minimal risk and the requirements for one or more of the expedited categories. Additionally, the IRB member(s) must determine that all the criteria for approval outlined in the regulations (*45 CFR 46.111, 21 CFR 56.111*) have been met:

1. Risks to subjects are minimized;
2. Risks to subjects are reasonable in relation to anticipated benefits;
3. Selection of subjects is equitable, by taking into account:
   a) The purpose of the research,
   b) The setting in which the research is being conducted,
   c) Whether prospective subjects would be vulnerable,
   d) The selection (*inclusion/exclusion*) criteria,
   e) Subject recruitment and enrollment procedures,
   f) The influence of payments to participants;
4. Appropriate informed consent will be sought from prospective subjects or their Legally Authorized Representatives (LARs);
5. Informed consent will be appropriately documented;
6. There are adequate provisions for monitoring data collected to ensure the safety of subjects (*when appropriate*);
7. There are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data (*when appropriate*).

4.5.3.6. IRB Review of Consent Documents:

The IRB member(s) also reviews the informed consent process and the informed consent document(s) to determine whether all the required elements of consent are present (*45 CFR 46.116,21 CFR 50.25*) and whether the consent process is appropriate. COM-R IRB expects informed consent documents for the general public to follow the appropriate health literacy standard. All forms should be written at a 5th to 8th grade reading level, as possible.

4.5.3.7. IRB Actions Under Expedited Review:

1. Approve as submitted;
2. Modification Required: Modification or additional information required to secure approval and the investigator's response may be reviewed through expedited review procedures;
3. Referred for convened IRB review: Either the research as submitted does not meet the requirements for minimal risk, the expedited review categories, or the IRB member(s) has concerns regarding the protocol and would like a convened review (*i.e., involves a vulnerable population, such as prisoners or the decisionally impaired*).

4. The IRB members may not disapprove a research protocol under expedited review procedures.

4.5.3.8. Documentation of Decision Under Expedited Review:

1. The determination of the IRB will be provided in writing to the investigator.
2. When the IRB approves the research, the IRB will also determine the interval of continuing review appropriate to the degree of risk. The federal regulations require that the approval period must be less than one year. Although the vast majority of minimal risk protocols have an approval period of 364 days, the IRB may assign shorter approval periods if they determine that it is appropriate for the research.
3. The investigator should be sure to note the expiration date of approval contained in the approval letter to ensure that the continuing review submission is submitted in the proper time frame to prevent a lapse in IRB approval.
4. The approval period will also be stamped on the consent document and all recruitment materials.
5. The investigator should use copies of the stamped consent and recruitment materials to enroll subjects in the research. The stamped documents will be provided to the PI along with an approval letter.

4.5.3.9. Decision Making Under Expedited Review:

1. Whenever subjects considered to be "vulnerable" under federal or state regulations or "vulnerable" to coercion or undue influence (*such as children, pregnant women, mentally disabled persons, economically or educationally disadvantaged persons*) are to be enrolled in the research, the IRB will make the additional determinations required by the regulations as to whether or not a given vulnerable population's involvement is adequately justified and whether additional safeguards should be included in the research to protect the rights and welfare of these subjects.
2. If a research protocol meets the requirement for "minimal risk" research, but includes activities outside of the expedited review categories, then the protocol must be reviewed by the convened IRB. Subsequently, at the convened meeting, the convened IRB has the option to make the determination that although the research includes activities outside of the categories eligible for expedited review, the research involves minimal risk and may be reviewed under expedited review in the future (*at time of continuing review, thus meeting the criteria for expedited category 9*). This determination can only be made by the convened IRB at the time of the initial review or possibly a subsequent continuing review.
3. COM-R HSPP policy does not require Departmental Review (*completion of Appendix F*) for expedited initial review protocols; however, Department head signature is required on all initial review applications.
    a) If the expedited review protocol involves cancer research or cancer patients from and is funded by the UIC Cancer Center, it will require Cancer Center Review. For further information about the Cancer Center and the protocol

review process, the investigator should refer to their web-site: http://www.uic.edu/com/cancer/.

b) There are no COM-R IRB requirements for formal Departmental Review at the COM-R campus. Please consult each college and department policy before submitting to the COM-R IRB to see if Appendix F is required.

4.5.3.10. Procedures for Expedited Review (*Initial and Continuing Review*):

1. Certain types of research protocols may be eligible for review under expedited review procedures. The research must involve no more than minimal risk and involve only procedures listed in one or more of the categories allowed for expedited review as specified in the regulations and in the federal register (*45 CFR 46.110, 21 CFR 56.110, 38 CFR 16.110. 63 FR 60364-60367, November 9, 1998*).

2. There are nine categories of research that have been determined by HHS as being eligible for expedited review procedures. Seven of these categories apply to initial review of research protocols and two categories (*categories 8 and 9*) apply only to the continuing review of research protocols. The seven initial categories are listed on the "Expedited Review Guide for IRB Members" and on the RSS "Initial Application" form (*either "Biomedical/Health Sciences" or "Behavioral/Social Sciences"*) the investigator submits to RSS for IRB review.

3. After determining whether or not the research involves minimal risk, the investigator may submit a new research protocol for review by specifying the relevant criteria/criterion that make(s) it eligible for expedited review. The IRB members may choose to review a research protocol under expedited procedures even if the investigator did not submit the research protocol for review for expedited review. IRB members can "bump" a review to convened meeting if they are uncertain regarding its appropriateness for expedited procedures.

4. For initial review and continuing review of research protocols, IRB members review the research application, protocol, consent document(s), and all supporting materials to determine if the research meets the definition of minimal risk and involves procedures that fall into one or more of the expedited categories. If the research is awarded a grant, contract, or cooperative agreement from an HHS agency and COM-R is the awardees' (*primary institution*), the IRB reviewers must have access to the entire application or proposal (*exclusive of apprendices*). If COM-R is not the awardee but a subcontractee, the portion of the HHS proposal relevant to COM-R's participation must be available.

   The research is considered to be no more than minimal risk when it is determined that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests" (45 CFR 46.102(i)). During the review process, IRB members may ask the RSS Specialist to contact the PI to ask questions or seek clarification about the research.

5. The reviewer(s) exercise the authority of the IRB in approving or requiring modifications to research in order for it to obtain approval when reviewing a research protocol under expedited procedures. If the reviewer(s) believe that there is reason for disapproval, or the nature of the project is not suitable for expedited review, then the reviewer(s) must defer any decision and refer the application for review at a convened IRB meeting.

6. If two or more IRB members conduct an expedited review and their determinations are not in agreement, the IRB Chair, or another IRB member designated by the Chair, will also review the research protocol for a final decision or refer the matter to a convened meeting of the IRB.

7. Under expedited review procedures, the IRB Chair, and designated experienced members may make the following determinations:
    a) Approve as submitted;
    b) Modifications or additional information required to secure approval and the investigators response may be reviewed through expedited review procedures.
    c) Refer for convened IRB review, either does not meet the requirements for minimal risk, the expedited review categories, or the IRB members have other issues with the protocol and would like a convened review.

8. IRB members have reviewer tools and guides available to assist them in ensuring that all criteria for approval are considered, met and documented. These reference resources should be used in guiding the decision making process concerning the Expedited Review submissions. Any comments and/or issues that require modifications or additional information must be detailed along with the determination of the IRB member, in writing. The RSS Specialist will take the details provided in the formal decision and provide that information to the investigator in a letter with instructions regarding how to respond to the IRB's request.

9. The COM-R IRB is informed of all research protocols reviewed and approved under expedited review procedures through inclusion of this information on the next available meeting agenda, and the information is documented in the corresponding meeting minutes in accordance with 45 CFR 46.110(c), 21 CFR 56.110(c), and 38 CFR 16.110(c). An approval of research by expedited procedures is complete by itself and does not require any ratification by the convened IRB. However, the IRB does have opportunity and the authority to raise questions about any research that was previously approved under expedited procedures, and to re-review those research protocols at a convened meeting if it chooses to do so. In accordance with 63 CFR 60364-60367, "Classified research" is not eligible for expedited review. Further, UIC IRBs do not review classified research and University of Illinois policy **prohibits** the conduct of classified research on University property.

4.5.3.11. Expedited Review of Amendments:

Amendments to the research may be reviewed under expedited review procedures, if the amendment is minor in nature and does not alter the research substantially or add additional risks to the research. This determination is made on a protocol by protocol basis. Examples of amendments that may be eligible for expedited review include:

1. Addition or revision of recruitment materials;
2. Addition of key research personnel may in some cases be eligible for expedited review:
3. The action of replacing a PI, such as a change to an inexperienced PI, is not considered minor and not eligible for expedited review.
4. Addition of a new site where research will be performed may in some cases be eligible for expedited review. (*The addition of a local site that often participates in research overseen by the COM-R IRB may, on a protocol by protocol basis, be considered minor, but the addition of a less familiar, distant, or international site might not*).
5. Grammatical revisions to the consent document;
6. Increasing subject enrollment total.

NOTE: *If the original protocol was approved via expedited review procedures, the amendment may be reviewed through expedited review procedures, unless the amendment alters the research by making it greater than minimal risk. If this were the case, the entire research protocol would then need to be moved to convened review.*

7. In reviewing the amendment, IRB members assigned to the review, must determine that all the criteria for approval outlined in the regulations (*45 CFR 46.111, 21 CFR 56.111*) continue to be met:
    a) Risks to subjects are minimized;
    b) Risks to subjects are reasonable in relation to anticipated benefits;
    c) Selection of subjects is equitable;
    d) Appropriate informed consent will be sought from prospective subjects or their Legally Authorized Representative (LARs);
    e) Informed consent will be appropriately documented;
    f) There are adequate provisions for monitoring data collected to ensure the safety of subjects (*when appropriate*);
    g) There are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data (*when appropriate*).

4.5.3.12. IRB Actions Reviewing Amendments Under Expedited Review:

The IRB reviewer assigned to review the amendment via expedited review may make the following determinations regarding the amendment:

1. Approve – no issues;
2. Modifications or additional information required;

3. Refer for convened IRB review.

NOTE: *If the amendment involves the addition of consent processes or HIPAA authorization processes that involve a waiver of informed consent, a waiver of documentation, or a waiver of authorization, it is possible the IRB member may also need to document the approval of that waiver and the protocol specific reasons why the waiver is approvable.*

4.5.3.13. Procedures for Expedited Review of Amendments:

1. The Investigator must conduct the research in accordance to the specific methods that were proposed in the application and/or protocol that was approved by the IRB. COM-RHSPP policy and the federal regulations require that the investigator report promptly to the IRB when there are proposed changes in a previously approved research project. In addition, it is required that any proposed changes in approved research, during the period for which IRB approval has already been given, are not initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards
   to the subject.

2. Minor Modifications to Previously Approved Research. The IRB may review minor changes in previously approved research during the period for which approval has been given, under expedited review procedures. A "minor change" is defined in this policy and COM-R practice as a change in the research plan that does not increase the risks related to the study (*including risks related to procedures and methods, and to modifications that might negatively impact the statistical analysis of the research*).

   If the change affects two of the following three aspects of the research, the change CANNOT be considered "minor" and MUST be reviewed by the convened IRB, unless the research was originally reviewed and approved via expedited review procedures.

   (i) The purpose,

   (ii) The population, or

   (iii) The procedures.

   Sometimes, an amendment may alter a minimal risk research study, such that it is no longer eligible for expedited review. If this is the case, then the IRB reviewer will refer the entire protocol with the amendment for convened IRB review.

3. Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more experienced reviewers designated by the Chair from among members of the IRB. The IRB Chair or experienced IRB members should utilize the review guide, after the submission has received a pre-review by the RSS Specialist, to ensure all criteria for review are considered, met and documented.

4. For amendment eligible for expedited review, the original reviewer(s) will be assigned to review the amendment. If they are unavailable the amendment will be re-assigned to a new reviewer or the Chair.

4.5.3.14. IRB Actions Reviewing Amendments Introducing Newly Required Waivers/Alterations of Consent or HIPAA Authorization:

1. Approve: Approved for implementation.
2. Modification Required: Modification and/or additional information is required to secure approval to implement.
3. Refer: Refer for review by convened IRB.

   NOTE: *If the amendment involves the introduction of newly required waivers or alterations of consent or HIPAA authorization, the IRB member must document these determinations. If the amendment involves the addition of a vulnerable population, the IRB members must document the required determinations for these populations.*

4.5.3.15. Procedures for Documentation of Amendments:

1. The COM-R IRB is informed of all amendments to previously approved research protocols reviewed and approved under expedited review procedures on the next available meeting agenda and this is documented in the IRB meeting minutes in accordance with 45 CFR 46.110(c) and 21 CFR 56.110(c).
2. The date of approval of an amendment does not change the original approval period or the expiration date by which the regularly scheduled continuing review of the research project should be done.

References:
21 CFR 56.110
38 CFR 16.110
45 CFR 46.110

4.5.4. Convened (*Full Board*) Review

It is the policy of the COM-R IRB to render determinations according to the Federal regulations.
The COM-R IRB uses a reviewer system with a first and second reviewer for reviewing the following: Initial, Continuing Review, and Amendments.

A. For FDA regulated studies, a licensed physician must be included in the IRB quorum for FDA research.

B. All IRB Members, alternate members, and *ad hoc* consultants are distributed all protocol materials specific to their review assigned to the meeting with sufficient time to review the materials in accordance with COM-R HSPP policy *IRB Meeting Frequency and Meeting Assignments.*

C. All IRB members are responsible for reviewing the agenda and determining whether they have a conflict of interest prior to the meeting.

D. Either one of the primary reviewers is responsible for presenting the protocol in summary form to the convened IRB highlighting any controverted issues and recommending modifications, if applicable. All reviewers should also use the appropriate review guide as a

tool to ensure that each regulatory element is addressed and are encouraged to use this tool to organize and/or edit his or her findings when addressing the convened IRB.

E. *Ad Hoc* Consultants invited to present information at the IRB meeting are present only for the discussion involving the relevant protocol, speak to the discreet area of knowledge in their written report, and remain present until the IRB is ready to vote to allow the IRB members to ask the *Ad Hoc* Consultant any questions or concerns that they might have before voting. *Ad Hoc* Consultants are not permitted to vote and do not count toward quorum. (Refer to COM-R HSPP policy *Identification and Use of Ad Hoc Consultants*.)

F. The IRB discusses each protocol individually and applies the criteria for approval as described in the appropriate review guide, which each IRB member should utilize while reviewing all materials.

G. Any IRB member who cannot attend the convened meeting may submit his or her written feedback by email or post their comments in the appropriate study packet on IRBNet so their comments can be shared with the committee. IRB members who do not attend the IRB meeting do not count toward quorum and cannot vote.

H. In instances where the IRB did not approve the study under review, the PI must respond to the IRB's determinations in writing. The IRB may also provide a PI with an opportunity to respond to the IRB in person at a convened IRB meeting. A PI may express interest to RSS staff to respond to the IRB in person, but whether or not the PI may attend is at the discretion of the Chair. Regardless of whether or not the PI attends the convened IRB meeting, RSS still requires a written response from the PI to the IRB's determinations.

I. The IRB must not grant final approval until other pertinent organizational committees that are required to review and approve the protocol has completed this task and the approval letter is provided to RSS by the PI (*i.e., RSC, IBC*).

J. The IRB determines the review interval appropriate to the degree of risk. The maximum length of IRB approval is 364 days.

K. All criteria for approval must be met and documented individually (*DHHS, FDA, and VA as applicable*). The Reviewers must detail how the criteria for approval are met and present this information to the panel. (*Refer to COM-R HSPP tool, policies and procedures, and review guides; Meeting Minute tool, Documentation of IRB and RSS Activities, and Initial Review Guide, Continuing Review Guide, Amendment Review Guide, or Final Review Guide, as appropriate*).

4.5.4.1. Range of Possible Actions for Convened IRB Review:

A. For each agenda item the IRB makes one of the following actions, which must be documented in the IRB meeting minutes in accordance with the COM-R HSPP policy *Documentation of IRB and RSS Activities* and communicated in the letter to the PI:

1. Approved: An approval is granted if the research activity meets the criteria for approval as defined in 45 CFR 46.111 as applicable and no changes to the research application is recommended (*DHHS, FDA, and VA, as applicable*).

2. Modifications Required: The RSS Specialist communicates in writing the modifications required by the IRB to a protocol. The investigator must complete the requirements, and the protocol must then be reviewed at the appropriate level.

3. Deferred: Deferred means the research does not meet the criteria for approval (*DHHS, FDA, and VA as applicable*). Protocols are deferred when they:
   (1) lacks sufficient information to conduct an adequate review, **or**
   (2) the IRB panel recommends revisions to the IRB application, protocol, informed consent document(s), or other pertinent documents rendering it unable to assess the risk/benefit analysis without the completed revisions.

4. Disapproved: A study is disapproved if it is found to be:
   (1) Unethical, **or**
   (2) Without scientific or scholarly merit, and/or
   (3) Does not meet the criteria for approval (*DHHS, FDA, and VA as applicable, see appropriate SOP*). Written notification from the IRB is to be provided to the PI for the decision with an invitation for a reply by the Investigator. The PI may be invited to submit a new protocol.

5. Tabled: A study is tabled if it is unable to be reviewed at the meeting due to lack of time, lack of quorum, lack of IRB panel expertise, and/or other extenuating circumstances.

6. Sponsor-Imposed Suspension: A sponsor-imposed suspension is when the IRB receives written notification from the Investigator that the sponsor has stopped the research study or portions of the research. This will be acknowledged by the IRB, the IRB Chair, or his/her Designee when the appropriate level of review determines the suspension is appropriate. Submit notice through the prompt reporting form.

7. Suspension: A suspension means a determination from the IRB to temporarily withdraw approval of all or some specific research activities, indicating that the specified activities must stop immediately.

   The appropriate party may impose additional criteria for suspension, if needed, to protect the participants from potential harm per the COM-R HSPP *Administrative hold, Suspension, or Termination of IRB Approval.* Suspended research projects still have IRB approval and require continuing review. For example, the IRB may stop the enrollment of new subjects, although may allow the continuation of currently enrolled subjects, if appropriate. The convened IRB would review the investigator's response, if any.

8. Termination: A termination means determination from the IRB to permanently withdraw approval of all research activities, indicating that the specified activities must stop immediately due to significant concerns. A convened IRB must review the PIs response, if any. The only exception for immediately

halting research is for the continuation of follow-up activities necessary to protect the participants' safety. Terminated research projects no longer have IRB approval and do not require continuing review. The COM-R HSPP policy *Administrative Hold, Suspension, or Termination of IRB Approval* must be followed.

4.5.4.2. Date of Approval and Expiration:

A. The IRB may require continuing review more frequently than once per year. Examples of studies that may require review more frequently than annually include (*but are not limited to*):
   1. Studies that pose a very high level of risk to individual participants (*very high risk to individuals*);
   2. High risk studies that are expected to have a large number of participants involved (*high cumulative risk*);
   3. Phase I drug and device studies;
   4. Investigator-initiated studies involving new technologies; and
   5. At its discretion, the IRB may require a more frequent review period than annually for studies conducted by PIs who have been non-compliant with the protocol at issue or other protocols, are currently involved in a for-cause compliance investigation, or studies being conducted by new investigators.

B. The expiration date is the last date that the research is approved. Federal regulations do NOT allow for any period extending the conduct of research beyond the last date that the protocol is approved (*no greater than 364 days*). Therefore, PIs and their staff should submit their continuing review application to RSS with sufficient time to allow for corrections, modifications, or deferral determinations, as required by the IRB, and to receive approval before the date of IRB approval expiration.
   1. Date of Expiration: The date of expiration stamped on the informed consent and indicated on RSS correspondence is the last date that the research is approved. For example, if the approval stamp states, "COM-R IRB Approval Starts from January 1, 2009 to December 31, 2009," the informed consent form and research protocol is no longer valid as of midnight December 31, 2009.

      If the investigator has not obtained continuing review approval by the expiration date, all research activities MUST stop. If a continuing review or final report submission is not provided within 30 days, the research protocol is terminated or withdrawn.

      Following the lapse of approval, the investigator must provide the IRB with a list that specifies the number of currently enrolled subjects, an assessment of the risk to subjects of stopping study activities and the need to continue any research interventions, or a signed assurance that no subjects are currently

enrolled in the research or at risk. Additionally, notification of the sponsor of any lapse of approval is typically required.

2. Date of IRB Approval. The approval date is the first date of approval for the protocol.

4.5.4.3. Post Meeting Activities:

A. The IRB notifies Investigators of the following:

1. Its decision to approve, disapprove, or require modifications to secure approval of research.
2. Its decision to defer the research for further review by the convened IRB or the decision to table the research for review at a subsequent IRB meeting.
3. Any modifications or clarifications required by the IRB as a condition for IRB approval.
4. When the IRB deferred the research for further review by the convened IRB or approve with modifications, a statement of the reasons for its decision.
5. Investigators are required to respond in writing and are given the opportunity to respond in person.

B. Additional approvals.

1. Research with prisoners, and review of research under 21 CFR 50.24, as well as other research not listed in this item, may require additional review and approval by the IO on a case by case basis.
2. Research involving children where there is no prospect of direct benefit to the individual child may require further review by a panel of experts convened by DHHS.
3. The Federal Bureau of Prisons places special restrictions on research that takes place within the Bureau of Prisons under 28 CFR 512. The provisions of 28 CFR 512 identify additional requirements for prospective researchers (*both employees and non-employees*), primarily to obtain approval to conduct research within the Bureau of Prisons, and outlines the responsibilities of Bureau staff in processing proposals and monitoring research projects.

4.5.4.4. Initial Review:

In accordance with federal regulation, COM-R policy requires that the IRB insure that certain criteria are met before approving a study. When reviewing each protocol a reviewer must use care and good judgment regarding issues such as the risk/benefit ratio, equitable selection of subjects, and the protections of any specially protected group according to federal regulations.

4.5.4.4.1. Evaluating Risk/Benefit Ratio:

COM-R IRB identifies risks in accordance with the criteria for IRB approval. The COM-R IRB evaluates risks, benefits, and the risk/benefit ratio for all research protocols that are reviewed, as applicable.

A. Regardless of funding source, the PI must submit the materials, or answer questions in sufficient detail, as required by the appropriate Initial Review Application form, Prompt Reporting Form, Amendment form, Continuing Review form, or Prompt Reporting form so that the IRB may make determinations as to the risks and the risk/benefit ratio of the research.

B. The IRB identifies and analyzes potential sources of risk and measures to minimize risk, including physical, psychological, social, legal, or economic risks. The IRB will evaluate the PI's submission using the appropriate review guide checklists applicable to the type of research [*DHHS, FDA, VA (which includes effects on insurability)*] to determine the following:

1. The IRB should consider risks and benefits that may result directly from the research. In most instances, speculation about the long-term effects of applying any knowledge that might be obtained from the research, such as the long-term effects on public policy, is likely outside the scope of the IRB review as to the risk/benefit analysis for most research topics that meet the requirements of *The Belmont Report*.

2. Risks to participants are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose participants to risk.

3. Risks to participants are minimized, when appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

4. Risks to participants are reasonable in relationship to the potential benefits, if any, to participants, and the importance of the knowledge that may be expected to result from the research.

C. The IRB also considers a wide range of benefits, including therapeutic, educational, informational, or broad empowerment benefits using the appropriate review guide checklists applicable to the type of research (*DHHS, FDA, VA*). Benefits may accrue to the participants or their community.

References:
21 CFR 56.111(a)(1), 21 CFR 56.111(a)(2)
38 CFR 16.111(a)(1). 38 CFR 16.111(a)(2)
45 CFR 46.111(1)(1), 45 CFR 46.111(a)(2)

4.5.4.4.2. Equitable Selection of Subjects:

Regardless of the funding source, the COM-R IRB must determine that the selection of subjects is equitable. The IRB must evaluate whether the research, including both the selection (*inclusion and exclusion criteria*) and the proposed recruitment plan in

the protocol, impose fair and equitable burdens and benefits to the participants. PIs must submit the materials, or answer the questions in sufficient detail, as requested in the appropriate application form for the IRB to make determinations as to whether the selection of subjects is equitable.

The IRB reviews whether the selection of subjects is equitable based on the materials submitted by the PI in the appropriate application form and through the use of the appropriate appendices. The IRB includes the following criteria in its evaluation:

A. The purposes of the research;
B. The setting in which the research would be conducted;
C. Whether the prospective participants would be vulnerable to coercion or undue influence;
D. The selection (*inclusion/exclusion*) criteria;
E. Participant recruitment and enrollment procedures; and
F. The influence of payments the amount and timing of payment to participants.

References:
21 CFR 56.1119a)(3)
38 CFR 16.111(a)(3), 38 CFR 17.45
45 CFR 17.92, 45 CFR 46.1119a)(3)
OHRP Guidance on Written IRB Procedures

4.5.4.5. Continuing Review:

In accordance with federal regulations, COM-R policy requires that IRB-approved research be reviewed at intervals appropriate to the degree of risk and at a minimum of once per year for both federally funded and non-federally funded research. Research that is not reviewed at least once a year is deemed to be lapsed in IRB approval and a notice of expiration of IRB approval must be issued.

An investigator may submit a request to RSS for a protocol exception after a study is deemed lapsed in IRB approval to allow follow up interventions or interactions for some or all subjects when it is in the best interest of the subjects to continue. The investigator requests a protocol exception for the continuation of certain aspects of the research on the COM-R RSS *Protocol Exception* Form. An investigator must clearly distinguish and explain what research activities from which he or she will refrain as part of the lapse and what research activities require continuation. The investigator must also explain the underlying reasons for which the protocol exception is requested for each activity and each subject where an over-riding safety concern or ethical issue indicates that it is in the best interests of the individual to continue participating. (*Refer to COM-R HSPP policy Protocol Exceptions*).

4.5.4.5.1. Initially Reviewed by Convened Review:

If a research study was initially reviewed by a convened IRB, and the IRB has not determined that the study is minimal risk and eligible for expedited review, then subsequent continuing reviews must be reviewed:

1) By a convened IRB (*refer to COM-R HSPP policy Expedited Review*) **or**

2) The research meets one of the following criteria:

- The research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; **or**
- Where no subjects have been enrolled at COM-R and no additional risks have been identified either at COM-R or at any site if the research involves a multi-site study; **or**
- The only remaining research activities are limited to data analysis. (*Refer to COM-R HSPP policy Expedited Review*).

4.5.4.6. Caution and Guide:

The convened IRB and IRB members (*expedited review*) should refer to the appropriate review guide to ensure that the regulatory requirements of continuing review are met (*Refer to COM-R RSS review guides and component guides: Initial Review Guide, Amendments Review Guide, Continuing Review Guide*, and *Final Report Review Guide*).

NOTE: *Research studies that once met exempt or expedited review standards may not change in nature without going through a formal amendment to the protocol.*

References:

21 CFR '56.108(a)-(a)-(2), 21 CFR 56.109, (f), 21 CFR 56.111
38 CFR 16.103(a), 38 CFR 16.111
45 CFR '46.103(b)(4)-(4)(ii), 45 CFR '46.109(e), 45 CFR 46.110, 45 CFR 46.111
63 FR 60364-60367; 63 FR 60353 – 60356;
DHHS-FDA List published in Federal Register November 9, 1998

4.5.5. Subsequent Reviews

Subsequent reviews are IRB reviews of a protocol AFTER the initial approval has been granted.

4.5.5.1. Amendments to the Protocol or Informed Consent Documents:

COM-R RSS reviews all amendment requests to previously approved research applications or exempt research to determine whether the amendment affects the risk/benefit analysis or exempt status of the research study.

Amendments for both federally and non-federally funded research must be approved by the IRB or the appropriate reviewer before the PI may implement the amendment. A PI may implement a change to the approved protocol prior to IRB approval only when necessary to avoid an immediate hazard to the subject.

A. The PI must submit a list of the revisions being requested and the reason for the changes using the COM-R RSS *Amendments to Previously Approved Research* form. The submission must also include a justification as to whether the amendment changes the risk/benefit analysis. If the PI believes that the risk/benefit analysis has changed to an extent that currently enrolled subjects and/or previously enrolled subjects must be re-consented, and subjects and/or previously enrolled subjects must be re-consented, and subjects who have completed participation must be informed, the PI must indicate this. The IRB or reviewer may also determine on this basis that currently enrolled subjects must be re-consented and subjects who have completed participation must be informed.

(1) If applicable, the PI must include a revised protocol, instruments (*survey, questionnaires, etc.*), informed consent, HIPAA Authorization, and/or recruitment materials that incorporate the changes.

(2) The PI must also submit a marked copy of all affected documents that has new wording highlighted and the old wording notated with a strikethrough on the original application and all appendices, consents, recruitment, or data collection instruments, etc. to indicate the modifications.

(3) The footer version and date of any documents affected by the amendment should be revised accordingly.

(4) If affected, the first page of the protocol should be revised accordingly, including the new footer version and date.

B. If affected, the original COM-R RSS *Initial Review Application: Health and Biological Sciences* Form or the *Initial Review Application: Social and Behavioral Sciences* Form or the Initial Review Application: Social and Behavioral Sciences Form should be revised accordingly, including the footer version and date.

C. When applicable, the PI must incorporate changes to the informed consent/informed consent process that affect the research protocol in the protocol document and submit this document as part of the amendment. All language that has been added should be highlighted in the original document to indicate the new language and any language that is being removed should be indicated by a strikethrough. This document should be identified as the highlight/strikethrough version.

D. The RSS Specialist reviews the following documents:

(1) Amendment application;

(2) Revised protocol, instruments (*survey, questionnaires, etc.*), informed consent, HIPAA Authorization, and/or recruitment materials that incorporate the changes;

(3) Review the marked copy of all affected documents with track changes;

(4) Review the footer version and date of any documents to ensure that any affected by the amendment was revised accordingly;

(5) Ensure that, if affected, the first page of the protocol was revised accordingly, including the new footer version and date; and/or

(6) Ensure that, if affected, the original COM-R RSS *Initial Review Application: Health and Biological Sciences* Form or the *Initial Review Application: Social and Behavioral Sciences* Form was revised accordingly, including the footer version and date.

E. Amendment submissions that include both minor and more than minor changes cannot be separated if combined into the same Amendment Application. Submissions that include both minor and more than minor changes must be reviewed by the convened IRB in their entirety.

F. The RSS Specialist should consult the IRB Chair whether the requested amendment constitutes a minor or more than minor change.

G. Minor changes may be reviewed in an expedited manner. Expedited review must be documented using the COM-R RSS *Amendment to Previously Approved Research Review Guide.*

H. Amendments to claims for exemption must be initially assessed at a minimum expedited procedures by an appropriate reviewer or referred to determine if the study still qualifies for exemption. If the proposed change no longer makes the research eligible from an exemption from IRB review, the research is referred for IRB review. (*Refer to the COM-R HSPP policy Exempt Review and the COM-RRSS Exempt Review Guide for more information*).

I. An amendment involving more than minor changes to the previously approved research must be reviewed and approved at a convened IRB meeting. (*Refer to the COM-R HSPP policy Convened Review and the COM-R RSS Convened Review Guide for more information*).

J. The IRB members, including alternate IRB members, review all modified documents in enough depth to discuss the information.

K. If a more than minor change is at issue, the convened IRB must consider whether the changes to research activities require changes to the informed consent forms and whether currently enrolled subjects and/or previously enrolled subjects must be re-consented. This determination should be based on whether new information affects the risk/benefit analysis in a way that could affect a subject's decision regarding willingness to participate or continue participation in the research study.

References:

21 CFR 50.25(b)(5), 21 CFR 56.108(a), 21 CFR 56.108(a)(3), 21 CFR 56.110(b)(2)
45 CFR 46.103(b)(4), 45 CFR 46.103(b)(4)(ii). 45 CFR 46.110(b)(2). 45 CFR 46.116(b)(5)
OHRP Compliance Activities: Common Findings and Guidance #5, #21, #71, #71(a), #73

OHRP Guidance on Written IRB Procedures
FDA Information Sheets: Continuing Review After Study Approval

4.5.5.2. Continuing Reviews:

In accordance with federal regulations, COM-R policy requires that IRB-approved research be reviewed at intervals appropriate to the degree of risk and at a minimum of once per year for both federally funded and non-federally funded research. Research that is not reviewed at least once a year is deemed to be lapsed in IRB approval and a notice of expiration of IRB approval must be issued.

An investigator may submit a request to RSS for a protocol exception after a study is deemed lapsed in IRB approval to allow follow up interventions or interactions for some or all subjects when it is in the best interest of the subjects to continue. The investigator requests a protocol exception for the continuation of certain aspects of the research on the COM-R RSS *Protocol Exception* Form. An investigator must clearly distinguish and explain what research activities from which he or she will refrain as part of the lapse and what research activities require continuation. The investigator must also explain the underlying reasons for which the protocol exception is requested for each activity and each subject where an over-riding safety concern or ethical issue indicates that it is in the best interests of the individual to continue participating (*Refer to COM-R HSPP* policy *Protocol Exceptions*).

4.5.5.2.1. Review Criteria:

If a research study was initially reviewed by a convened IRB, and the IRB has not determined that the study is minimal risk and eligible for expedited review, then subsequent continuing reviews must be reviewed by a convened IRB (*refer to COM-R HSPP policy Expedited Review*) or the research meets one of the following criteria:

(1) The research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; **or**

(2) Where no subjects have been enrolled at COM-R and no additional risks have been identified either at COM-R or at any site if the research involves a multi-site study; **or**

(3) The only remaining research activities are limited to data analysis (*Refer to COM-R HSPP policy Expedited Review*).

Research studies that once met exempt or expedited review standards may change in nature (*i.e., changes in the protocol which may alter the risks and/or benefits*) such that convened review may be required. (*Refer to COM-R HSPP policies Expedited Review, Exempt Review of Research; and Convened IRB Review Process*).

The convened IRB and IRB members (*expedited review*) must use the appropriate review guide to ensure that the regulatory requirements of continuing review are met. (*Refer to COM-R RSS review guides and component guides: Initial Review Guide, Amendments Review Guide, Continuing Review Guide, and Final Report Review Guide*).

References:
21 CFR '56.108(a)-(a)-(2), 21 CFR '56.109, (f), 21 CFR 56.111
38 CFR 16.103(a), 38 CFR 16.111
45 CFR '46.103(b)(4)-(4)(ii), 45 CFR '46.109(e), 45 CFR '46.110, 45 CFR 46.111
63 FR 60364-60367; 63 FR 60353 – 60356;
DHHS-FDA List published in Federal Register November 9, 1998

4.6. Other IRB Issues

4.6.1. Recruitment, Advertising, and Subject Payment

The COM-R IRB reviews proposed subject recruitment methods, advertising materials, and participant payment arrangement, and permits them when they are equitable, fair, honest, and appropriate. The IRB Chair, IRB member designee, or the convened IRB review the following to ensure the rights and welfare of the prospective subjects are protected:

A. The information that will be contained in the advertisement.

B. The mode of their communication. The final version of advertisements in any format; print, audio, video, or internet.

C. The information contained in the appropriate application form. The prorated reimbursement schedule based on the subjects' participation.

4.6.1.1. Recruitment Process.

The IRB, IRB Chair, IRB member designee, or convened IRB reviews whether the proposed recruitment of faculty, students, and employees as are the targeted research population when making its determination for approval in accordance with the appropriate review guide.

4.6.1.2. Recruitment Materials.

The IRB reviews the advertisement and other materials in accordance with the appropriate review guide. For additional information, refer to the COM-R HSPP Tip Sheet Recruitment Materials for Human Subject Volunteers, available at:
http://rockford.medicine.uic.edu/Research/research_support_services/human_subjects_research__irb_/i_r_b_required_documents/i_r_b_forms_and_appendicies/

4.6.1.3. Payment Plans.

A. The PI is responsible for accurately disclosing all information as to payment and including a prorated schedule of payments, as applicable, in the protocol application and the informed consent document in the appropriate application.

B. The PI must disclose any changes to the payment terms and submit changes to the IRB, IRB Chair, designee, or convened IRB through an amendment. The change in the payment terms must be approved and the PI must receive confirmation of approval before any changes in the payment terms can be implemented.

C. The IRB reviews the payment plan in accordance with the appropriate review guide.

D. If applicable, PIs must review the informed consent document content requirements for reporting payments greater than $600/calendar year to the IRS on the appropriate review guide.

E. For additional information, refer to University policy Human Subject Payments, available at: http://www.obfs.uillinois.edu/manual/central p/sec8-10.html

4.6.1.4. VA Research.

The IRB, IRB Chair, or designee, must prohibit proposed payments to VA research subjects that are not in accordance with the payment requirements of VHA Handbook 1200.05 as listed in the appropriate review guide. For details please review the VHA Handbook at: http://www.research.va.gov/programs/pride/policy/default.cfm

4.6.1.5. Department of Defense Sponsored Research.

If the Department of Defense sponsored research includes US Military personnel, the following recruitment limitations apply:

A. Limitations on dual compensation for US military personnel prohibits an individual from receiving pay from more than one position for more than 40 hours of work in one calendar week.

B. The above limitation includes temporary, part-time, and intermittent appointments.

4.6.2. Observation of Informed Consent:

In accordance with the federal regulations, COM-R IRB has the discretion of requesting that a third party observe the informed consent process. The COM-R IRB also has the discretion of appointing an ombudsman to oversee the research process in cases where the subject is particularly vulnerable or becomes incapacitated during the research study.

A. Third Party Observer to the Informed Consent Process -The IRB Chair, Vice Chair, or convened IRB may appoint an unbiased individual as a third party to observe the informed consent process on behalf of the IRB. The individual may monitor the process of informed consent conducted by the PI (*or a member of the IRB approved research staff delegated this role by the PI*) with the prospective research participant or the participant's legally authorized representative.

B. The third party may collect data on the informed consent process by employing a variety of methods, including but not limited to, a physical presence (*monitoring*) during the consent process and/or employing written and verbal questionnaires to evaluate the effectiveness of the consent process. For additional information regarding the direct monitoring of the consent process refer to the Standard Operating Procedure – Procedure for Observation of the Consent Process.

C. The IRB Chair, Vice Chair, or convened IRB may appoint an unbiased individual to act as a subject advocate or a liaison between the PI and the research subject, the subject's family, or the subject's legally authorized representative. The UIC Clinical Research Center (CRC) has a Research Subject Advocate who functions as an ombudsman for all research studies conducted within the UIC CRC. (*The CRC does provide services to the Rockford campus to assist in setting up and running clinical research protocols*);

D. The IRB Chair or Convened IRB may appoint an unbiased ombudsman specializing in a vulnerable population to oversee the research process, typically a scientist or an individual with expertise in the research area. This individual would observe the ongoing consent process and study conduct if the subject has become incapacitated during his or her research participation; or

E. The IRB Chair or Convened IRB may also appoint an unbiased ombudsman to oversee that a subject who is particularly vulnerable receives equitable and ethical treatment throughout the course of the research study. This type of ombudsman should have experience with the vulnerable population at issue or may also be a group of people with an interest in the safety of human research subjects, generally with a particular research focus. This type of ombudsman is permitted to be an IRB member, affiliated with COM-R.

References:
21 CFR 56 109 (f)
38 CFR 16.103(e)
45 CFR 46.109(e)

4.7. IRB Decisions and Actions

The IRB has the authority to suspend or terminate their approval of research that is not being conducted in accordance with IRB requirements or federal regulations, when the research is associated with unexpected serious harm to research participants or others or when there are immediate serious issues involving participant and/or others safety.

The IRB Chair, IRB members designated by the Chair, and IO has the authority to suspend previously approved research when required for the urgent protection of the rights and welfare of participants and insufficient time exists for the convened IRB to review the event. Any suspension of research by the above individuals is placed on the agenda and reviewed and upheld, overturned or supplemented by the convened IRB at their next meeting. That previously approved research may only be terminated by the convened IRB, including protocols originally approved under expedited procedures.

4.7.1. Administrative Hold, Terminations, Expirations:

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects or others. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Department or Agency head [*45 CFR 46.113, 38 CFR 16.113*] or Food and Drug Administration [*21 CFR 56.113*] (*University Department Heads may be included in reporting, as applicable*).

Definitions:

A. SUSPENSION: A suspension means a determination from the IRB to temporarily withdraw approval of all or some specific research activities or permanently withdraw approval of some specific research activities, indicating that the specified activities must stop immediately. The appropriate party may impose additional criteria for suspension, if needed, to protect the participants from potential harm per the COM-R HSPP policy *Administrative Hold,*

Suspension, or Termination of IRB Approval. Suspended research projects still have IRB approval and require continuing review. For example, the IRB may stop the enrollment of new subjects, although may allow the continuation of currently enrolled subjects, if appropriate. The convened IRB would review the investigator's response, if any.

B. ADMINISTRATIVE HOLD: An administrative hold is a voluntary action by an investigator or sponsor to temporarily or permanently stop some or all research activities as a modification to approved research. Administrative holds are not considered suspensions or terminations, and do not meet reporting requirements to OHRP, FDA and other federal agencies. Although the investigator may discuss this action beforehand with the RSS STAFF or IRB Chair, the hold must be initiated voluntarily by the investigator and must not be used to avoid IRB mandated suspension or termination or reporting requirements. During administrative hold, the research remains subject to continuing review and requirements for reporting non-compliance and unanticipated problems involving risks to subjects or others.

C. TERMINATION: A termination represents a directive from the IRB to permanently stop all previously approved research activities.

4.7.2. Administrative Hold:

A. Investigator informs the IRB of the request for administrative hold by submitting to RSS the COM-R RSS *Prompt Reporting to the IRB* form.
The investigator:
   1. Explains the event or reason triggering the administrative hold and whether the hold is initiated by the investigator or the sponsor of the research;
   2. Describes the research activities to be stopped (*e.g., recruitment; enrollment, interventions or interactions, follow-up or all*);
   3. Indicates number of subjects currently enrolled and proposed actions to protect their rights and welfare during the hold; and
   4. Describes plans for implementing the proposed actions, reporting to the IRB, and rescinding the administrative hold.

B. The RSS Specialist, in consult with the IRB Chair, reviews the form for completeness, contacts the investigator if necessary for additional information and makes a preliminary assessment of whether the request for administrative hold is appropriate.

C. If action is needed before the convened IRB meeting, the request is referred to the IRB Chair or designee. If not, it is added to the agenda of the next meeting. The action of the IRB chair or designee is reviewed by the convened IRB at the next meeting.

D. The minimum materials provided to the IRB (*or IRB chair or designee*) for review and evaluation of the request for administrative hold include:
   1. COM-R RSS *Prompt Reporting to the IRB* form;
   2. Any follow-up information gathered by the RSS staff or Chair;
   3. Current approved research protocol;

4. Current approved consent document; and
5. Access to the complete research protocol file.

E. Determinations that may be made by the IRB (*or IRB Chair or designee*) include:
   1. Approval of the administrative hold and action plan provided by the investigator;
   2. Approval of the administrative hold following acceptance by the investigator of additional IRB-mandated corrective actions;
   3. Request for further information;
   4. Disapproval of the administrative hold;
   5. Whether or not the event represents an unanticipated problem involving risks to subjects or others or serious or continuing non-compliance;
   6. Suspension or termination of part or all of the research.

F. Actions implemented by the IRB (*or IRB Chair or designee*) to ensure the rights and welfare of subjects may include:
   1. Notification of subjects of the administrative hold through oral or written communications approved by the IRB;
   2. Other measures to protect the rights and welfare of subjects and ensure the safe withdrawal of subjects (*e.g., more frequent monitoring of research or consent process*).

G. The investigator must submit an amendment to the IRB lifting the hold and obtain approval prior to the resumption of any activities restricted by the administrative hold.

4.7.3. Suspension:

A. Suspension of approved research by the IRB may arise from an evaluation of unanticipated problems involving risks to subjects or others, substantive allegations of serious or continuing non-compliance, or findings arising from continuing review or monitoring of research activities.

B. The review process depends on the event (*i.e., unanticipated problem/event, non-compliance*) triggering the determination of suspension. Minimum materials provided to the IRB (*or IRB chair or designee*) include:
   1. Report of event prompting consideration of suspension;
   2. Any follow-up information gathered by RSS staff or Chair;
   3. Current approved research protocol;
   4. Current approved consent document; and
   5. Access to the complete research protocol file.

C. The IRB (*or IRB Chair, designee, or IO*) determines and documents whether or not to suspend the research, the reason for suspending the research and the activities to temporarily stop (*e.g., recruitment, enrollment, some or all interventions or interactions, follow-up, data analysis or all research activities*).

D. When approval of all or part of the protocol is suspended, the IRB (*or individual ordering the suspension*) considers actions to protect the rights and welfare of currently enrolled subjects, including, but not limited to:
    1. Notification of subjects of the suspension through oral or written communications approved by the IRB;
    2. Allowing currently enrolled subjects to continue if it is in their best interest;
    3. Changes to the protocol, consent form or other documents to correct any deficiencies and protect the rights and welfare of subjects;
    4. Procedures for withdrawal of current subjects, when necessary, that take into account their rights and welfare, such as:
        a) Transfer of subjects to another investigator;
        b) Arrangement for clinical care outside of the research;
        c) Continuation of some research activities under the supervision of an individual monitor;
        d) Permitting follow-up for safety reasons.
    5. Follow-up procedures permitted or required by the IRB; **or**
    6. Requiring the reporting of unanticipated problems involving risks to subjects or others.

E. The IRB notifies the PI in writing of the suspension. The communication contains:
    1. Description of the research activities that are suspended;
    2. Reasons for the suspension;
    3. Corrective actions mandated by the IRB and measures needed to lift the suspension;
    4. A request for the number of currently active subjects and any measures needed to protect their rights and welfare is some or all research activities are stopped;
    5. Timelines for implementing the proposed actions and follow-up reporting to the IRB;
    6. Notification that any request by the investigator for the IRB to reconsider the suspension should be submitted within 30 days.

F. When the PI has addressed the concerns, the convene IRB may lift the suspension. If the concerns are not addressed, the IRB may terminate the research or take other action to protect the rights and welfare of subjects or others (*e.g., make a finding of serious or continuing non-compliance*).

4.7.4. Terminations:

A. Termination of approved research by the IRB may arise from an evaluation of unanticipated problems involving risks to subjects or others, findings of serious or continuing non-compliance, or findings arising from continuing review or monitoring of research activities.

B. The review process depends on the event (*i.e., unanticipated problem/ event, non-compliance*) triggering the determination of termination. Minimum materials provided to the IRB:
    1. Report of event prompting considering of suspension;
    2. Any follow-up information gathered by RSS Specialist or Chair;
    3. Current approved research protocol;
    4. Current approved consent document; and
    5. Access to the complete research protocol file.

C. The IRB determines and documents whether or not to terminate the research and the reason for terminating the research.

D. The IRB considers actions to protect the rights and welfare of currently enrolled subjects or others, including, but not limited to:
    1. Notification of subjects of the termination through oral or written communications approved by the IRB.
    2. Procedures for withdrawal of current subjects, when necessary, that take into account their rights and welfare, such as:
        a) Transfer of subjects to another investigator;
        b) Arrangement for clinical care outside of the research;
        c) Continuation of some research activities under the supervision of an individual monitor;
        d) Permitting follow-up for safety reasons.
    3. Follow-up procedures permitted or required by the IRB;
    4. Requiring the reporting of unanticipated problems involving risks to subjects or others if follow-up procedures are permitted.

E. The IRB notifies the PI in writing of the termination.
The communication contains:
    1. Reason for the termination;
    2. Corrective actions mandated by the IRB;
    3. A request for the number of currently active subjects and any measures needed to protect their rights and welfare if some or all research activities are stopped;
    4. Timelines for implementing the proposed actions and follow-up reporting to the IRB;
    5. Notification that any request by the investigator for the IRB to reconsider the termination should be submitted within 30 days.
    6. If the investigator wishes to pursue re-starting the research, he/she must address all concerns noted by the IRB and then re-submit a new proposal for IRB review and approval.

4.7.5. Reporting Policy for Suspension and Termination:

A. The communication to the PI is sent within 10 working days and copied to the Academic Department Head other relevant COM-R oversight committees (*e.g., FDA, Institutional Biosafety Committee, Radiation Safety, Cancer Center*).

B. The suspension or termination is promptly reported by the IO and federal agencies as described in the COM-R HSPP policy, Reporting requirements to IOs, supporting agency heads, and regulatory agencies for unanticipated problems/events requiring prompt reporting, serious reporting, serious or continuing non-compliance, and suspensions or terminations.

References:

21 CFR 56.108(b)(3), 21 CFR 56.113

38 CFR 16.103(b)(5)(ii), 38 CFR 16.113

45 CFR 46.103(b)(5)(ii), 45 CFR 46.113

4.7.6. Complaints, Feedback:

Federal regulations [*45 CFR 46.103(b)(5); 21 CFR 56.103(b), and 38 CFR 16.103(b)(5)*] require each institution to have ". . . written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i)…any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval." This document describes COM-R's policy and procedures for addressing complaints and allegations of potential non-compliance with Federal and State regulations, with University policies regarding research, and with the requirements of the HSPP.

It is COM-R policy that investigators, research team members, faculty and staff must report any allegations or observations of non-compliance in human subject research. Complaints or allegations of noncompliance may be directed to the RSS, IRB, UIC Associate Director of Research Compliance, Chair or IO. Research subjects and individuals not directly involved with conducting or overseeing the research are also encouraged to report suspected non-compliance.

This policy is applicable to all human subject research activities of COM-R faculty, staff, students, or others within the jurisdiction of the COM-R HSPP. The policy extends to adjunct and/or volunteer faculty when there is intention of utilizing their faculty appointment to the University in a publication, or when their appointment is listed among the investigator's credentials in study documents.

The COM-R IRB is responsible for ongoing monitoring of the safety and welfare of human subjects. Part of this monitoring is ongoing review and assessment of unanticipated problems involving risks to human subjects or others (UPIRSOs) related to participation in the research (*frequently called adverse events (AEs)*). The COM-R IRB, or designated members from the COM-R IRB, reviews the AE report when there are serious and unanticipated risks identified in the report.

PIs are required by federal regulations and COM-R policy to promptly report to the IRB all unanticipated problems in research involving subjects or others. Unanticipated deaths during

research studies should be reported within 24 hours of discovery of the event. Other serious and unanticipated adverse events should be reported within 10 working days.

All AE reports are initially assessed by the RSS staff upon receipt and all serious (*death, hospitalization, or any intervention to prevent irreversible morbidity or mortality, birth defects, or other serious harms, etc.*) and unanticipated (*not specifically included in the consent document, or exceeding the frequency or severity reported in the protocol or Investigator Bro*chure) events may be referred to review by the COM-R IRB at a convened meeting.

Designated members of the IRB review all reports of serious but anticipated, or unanticipated but not serious events, and determined whether or not the information needs to be reviewed at a convened meeting.

Definitions:

A. ALLEGATION OF NON-COMPLIANCE: An assertion of non-compliance.

B. CONTINUING NON-COMPLIANCE: Pattern of actions or omissions that suggests the likelihood of recurrence of non-compliance without intervention, or a failure to comply with a directive from the IRB to address an episode of compliance.

C. COMPLAINANT: Any individual(s) who makes a complaint to the IRB or makes an allegation of non-compliance.

D. FINDING OF NON-COMPLIANCE: A determination that non-compliance has occurred.

E. NON-COMPLIANCE: Conducting research involving human subjects in a manner that intentionally or unintentionally fails to comply with federal or state regulations, COM-R HSPP policies, or the requirements or determinations of the IRB. Examples include, but are not limited to, initiating research prior to IRB approval, implementing changes in the IRB-approved protocol without prior IRB approval, using inadequate procedures for informed consent, failing to meet education and training requirements and lapses in IRB approval.

F. RESPONDENT: The individual(s) about whom an allegation of non-compliance is made or the person(s) subject to an inquiry or investigation.

G. SERIOUS NON-COMPLIANCE: Non-compliance that has the potential to increase risk (*physical, psychological, economic, or social harm*) to research participants, compromise participants' rights or welfare, or affect the integrity of the research or the HSPP.

4.7.6.1. Reporting Occurrences or Allegations:

A. Investigators are required to promptly report all findings and allegations of noncompliance, including protocol violations to the IRB using the *Prompt Reporting to the IRB* form. The timeframes for reporting are within 10 working days of becoming aware of the event. These timeframes may be extended by the Chair and/or the IO under extenuating circumstances.

B. Non-compliance may be uncovered by the IRB, the RSS Specialist, or the IO (*e.g., during ongoing review or monitoring of research or through audits or other quality assurance activities*). These findings are forwarded through the IRB Chair or

convened IRB depending on their seriousness and the immediacy of potential harm or risks to research participants.

C. Allegations of non-compliance may also be reported by members of the research team, COM-R faculty, staff or administrators, sponsors, study participants, participating organizations, or other knowledgeable parties.

The complaints or allegations may be provided to RSS, IRB Chair (*or designee*), or IO. To facilitate reporting, informed consent documents provide a contact phone number and e-mail to discuss concerns or complaints with the research with RSS. The RSS website also provides telephone and e-mail contacts for the RSS Specialist.

4.7.6.2. Receipt and Initial Review of Allegations of Non-compliance:

A. When complaints or allegations of non-compliance are received via telephone, in person, or e-mail by the RSS Specialist from sources outside of the research team, the information is recorded on the *Complaint / Unanticipated Problem / Event Record – Transcription Form* and forwarded to the Chair of the IRB.

B. The Chair reviews the report for completeness, contacts the investigator (*if necessary*) for additional information and makes a preliminary assessment of whether the event represents non-compliance. ***NOTE:*** *If the investigator is unable or unwilling to work with the IRB Chair, then the Non-compliance is handled as continuing non-compliance.*

C. If the Chair finds the incident does not require the attention of the convened IRB, the Chair will then assess:

1. The effect of the AE on the risk-benefit relationship associated with the research (*i.e., no change in risks or benefits: increased risks with no change in benefits; or increased risks with decreased benefits*);
2. Whether the research protocol requires modifications;
3. Whether the informed consent process and/or informed consent document requires modifications to inform currently enrolled subjects or subjects who have completed their research participation;
4. Whether frequency of continuing review should be increased;
5. Whether additional safeguards should be implemented to minimize risk and/or maximize the potential for benefit.
6. Send the report of non-compliance, his/her findings, and corrective action report to the IO and provide the details at the next convened IRB meeting.

4.7.6.3. Convened IRB Review:

A. When an allegation of non-compliance issue is reviewed by the convened IRB two primary reviewers are assigned to conduct a thorough review of the packet of information and present the compliance issue to the full board. The IRB members receive at a minimum:

1. Original report of non-compliance;
2. Follow-up information gathered about the non-compliance issue;
3. Protocol summary;

B. When the Chair refers the AE to the convened IRB for review, the IRB may:

1. Acknowledge that the risk-benefit relationship has not changed and continue monitoring the research at the current continuing review interval;
2. Request further information from the PI;
3. Require revisions to the research protocol and/or informed consent document(s) or require an addendum to the informed consent document(s) to notify currently enrolled subjects of the situation so they may decide whether they wish to continue participation;
4. Require revisions to the research protocol and/or informed documtns or process for enrollment of new subjects;
5. Require notification to be sent to subjects who may have completed their participation in the research;
6. Reassess the period of COM-R IRB approval (*decreasing the time interval for continuing review reporting and COM-R IRB review*);
7. Implement additional safeguards (*i.e., more frequent specific monitoring*);
8. Suspend enrollment of new subjects;
9. Refer for further review as potential non-compliance;
10. Terminate the research.

C. The AE and corrective action report is then forwarded to the IO

D. Referral to other COM-R officials or committees for possible review.

4.7.6.4. Documentation and Follow-up:

A. The corrective action plan should include timelines for the investigator to respond to the IRB and follow-up evaluation of the implementation and completion of the actions by the investigator.

B. Review of the non-compliance issue is documented in the IRB meeting minutes.

C. A communication documenting the IRB's determination, the reason for the determination and the corrective action plan is generated and sent to the investigator within 10 working days of the convened IRB's determination. Copies of the communication are sent to the Academic Department Head, other relevant COM-R oversight committees (*e.g., RSC, CC)*.

D. Serious or continuing non-compliance is reported by the RSS to appropriate IO and federal agencies.

E. Reports to IO, OHRP, FDA and other federal agencies will be made promptly. In the event a situation requires extended time to investigate or resolve a preliminary report will be sent and followed by a final report. In no event will a preliminary report to IOs, the supporting agency head, or OHRP be delayed beyond 30 days of the RSS receiving notice of a reportable event.

4.7.6.5. Non-Compliance Investigation:

After providing the respondent an opportunity to appeal, the Chair issues his/her findings and recommendations in writing to the IO, the IRB, and the respondent. Recommendations may include, but are not limited to:

A. Dismissal of the allegations as unjustified, without merit or unfounded;

B. Resolution through corrective actions, such as an educational intervention or the addition of safeguards to the research, including the submission of the information to the IRB for approval of a protocol specific corrective action plan;

C. Increased monitoring where the transgression was minor and easily remedied;

D. Referral to form a Human Subject Investigation Committee (HSIC) for a formal investigation when the alleged complaint is founded and is of a potentially serious nature;

E. Referral of non-protocol specific sanctions for consideration by the IO;

F. Referral to the appropriate COM-R or COM-R or UIC officials or committees for resolution (*e.g., grievance, research misconduct*), if necessary. Based on the initial report, the IO or IRB Chair may institute immediate corrective actions prior to review by the convened IRB to protect the rights or welfare of the subjects, preserve the integrity of the study, or protect the integrity of HSPP.

4.7.6.6. Human Subject Investigative Committee (HSIC):

A. Composition. The HSIC includes a minimum of five faculty members, appointed by the IO, the IRB Chair and one IRB member. The HPA or designee serves as the non-voting Chair, and the UIC Associate Director for Research Compliance, and university legal counsel serves as ex-officio members. Other individuals may be appointed to the HSIC by the HPA or IO or serve as *ad hoc* consultants, as appropriate. No individual on the HSIC or serving as an *ad hoc* consultant should have a real or perceived conflict of interest with the research or review of the non-compliance issue under question.

B. Process. The HSIC, convened at the request of the Chair, the HPA, the IO or IRB will conduct an investigation. The Chair of the HSIC and the IO shall determine if additional consultants with special needed expertise should be appointed to the HSIC. The respondent will be given an opportunity to submit written comments or appear personally before the Committee. During any personal appearance, the respondent may be accompanied by an advisor of his/her choice. The person may advise, but not represent the respondent. When another individual will accompany the respondent, the HSIC must be notified at least five working days prior to the meeting and identify

whether the advisor is an attorney. If the respondent chooses an attorney for this purpose, a representative from the Office of University Counsel will be invited to be present to advise the HSIC. The respondent may also present relevant information and recommend additional individuals to be interviewed. At the conclusion of the investigation, the HSIC shall issue a written report summarizing the information examined, stating its conclusions and recommending the actions that the Committee deems appropriate. If the Committee decision is not unanimous, the report shall include a summary of the dissenting opinions. Generally, the HSIC investigation process should be completed within 60 working days from the time that the HSIC is convened. If during its investigation, the HSIC determines that it has not been able to adequately investigate the allegation of non-compliance, the HPA will be notified.

The HSIC shall:

a) Receive allegations of non-compliance or harm referred from the Chair or IRB;

b) Review the respondent's written response to the complaint or allegation;

c) Request and review other information, data, and materials relevant to the matter;

d) Interview individuals with information relevant to the research or instance of non-compliance at issue, including but not limited to, the complainant, if identified, research staff, and other investigators as needed; and

e) Seek other institutional resources or external consultants to provide expertise beyond that available on the HSIC as needed.

C. Recommendations. Following the completion of the HSIC's investigation, the Committee provides the respondent and the IO with its findings and commendations. After giving the respondent an opportunity to appeal, the HSIC issues its findings and recommendations in writing to the IO, the IRB, the respondent, other IOs as deemed appropriate, and, if appropriate, legal counsel. Recommendations may include, but are not limited to:

a) Dismissal of the allegation as unjustified, without merit or unfounded;

b) Resolution through corrective actions, such as an educational intervention or the addition of safeguards to the research, including the submission of the information to the IRB for approval of a protocol specific corrective action plan;

c) Increased monitoring where the transgression was minor and easily remedied;

d) Referral of non-protocol specific sanctions for consideration by the IO;

e) Referral to the appropriate COM-R or UIC officials or committees for resolution (*e.g, grievance, research misconduct*), if necessary. Based on the HSIC report, the IO or IRB Chair may institute immediate corrective actions prior to review by the convened IRB to protect the rights or welfare of the subjects, preserve the integrity of the study, or protect the integrity of HSPP.

4.7.6.7. Appeals Committee:

A. Composition. The Appeals Committee includes a minimum of three members; at least one faculty member and the IRB Vice-Chair, none of whom participated on the original decision or the HSIC. The Committee may consult University legal counsel as appropriate. Other members may be appointed by the IO to the Appeals Committee as appropriate. No individual on the Appeals committee should have a real or perceived conflict of interest with the research or review of the non-compliance issue under question.

B. Process. Once the Chari, IRB, or HSIC completes its evaluation, the findings and recommendations are provided to the IO and to the respondent. The respondent has 10 working days upon receipt of this report in which to appeal in writing to the Chair, IRB, or the HSIC.

The Appeals Committee reviews an appeal by the respondent and issues its recommendation as to whether reconsideration of the decision is warranted to the HPA, and IO. In the appeal, the respondent must provide a reason for the appeal, including the provision of new information and/or a request for a meeting with the Appeals Committee. The grounds for appeals by the respondent are limited to the following situations:

a) The respondent has new information that was unavailable at the time of the investigation;

b) The procedures outlined in this policy were not followed;

c) The sanctions are considered to be excessive.

The Appeals Committee will review the written appeal received from the respondent. If the respondent claims new, previously unavailable information was not considered, the Committee shall consider the information in conjunction with the report of original review or the HSIC. The Appeals Committee may meet with the respondent, the Chair, IRB or the HSIC in making its determination. The respondent shall have an opportunity to appear before the Appeal Committee if requested in writing. During any personal appearance, the respondent may be accompanied by an advisor of his/her choice. The person may advise, but not represent the respondent. When another individual will accompany the respondent must notify the Appeals Committee at least FIVE working days prior to the meeting and identify whether the advisor is an attorney. If the respondent chooses an attorney for this purpose, a representative from the Office of University Counsel must be invited to be present to advise the Appeals Committee. The respondent may present relevant information and recommend additional individuals to be interviewed. Generally, the Appeals Committee will make its final determination within 30 working days of receiving the respondent's request for reconsideration.

C. Outcome.

a) Recommendation that the appeal should be denied. If the Appeals Committee denies the appeal, the committee will recommend that the IO accepts the recommendations of the HSEIC or the HSIC as final.

b) Recommendation that the appeal be granted.

1) If the Appeals Committee recommends reconsideration, the Appeals Committee may recommend that the IO direct the Chair, IRB, or the HSIC to re-open the case to reconsider the matter in its entirety.

2) The Appeals Committee may recommend that the IO appoint a new HSIC to reconsider the matter.

The determination of the IO, based on the recommendation of the Appeals Committee, or referred decisions from the Chair, IRB, or the HSIC, will be presented in writing to the respondent within 10 working days of its decision and shall be final immediately. This decision will also be shared with the IRB, which may choose to take additional independent action.

4.7.6.8. Roles of the IO and the IRB:

A. No other entity within the COM-R may override a decision by the IO (*through the HSEIC or HSIC or the Appeals Committee*) that limits, imposes conditions or in any way restricts an investigator's privileges, or imposes conditions or restrictions upon an investigator or their research.

B. Likewise, no other entity, including the IO, may override determinations or corrective actions related to the investigator's human subject research protocols imposed by the IRB that limits, imposes conditions or in any way restricts an investigator's research protocols.

4.7.6.9. Confidentiality and Retaliation:

A. The prompt review of complaints and allegations of non-compliance is critical for maintaining the integrity of COM-R's HSPP and the IRB's ability to protect the human research subjects. A climate free from fear of sanction is required to foster reporting and ensure a fair review of complaints and allegations.

Retaliation against any person who in good faith reports potential non-compliance (*i.e., "whistleblower"*) is prohibited. Whistleblowers who report human subject protection concerns also have access to other mechanisms at COM-R for protection from retaliation under The State Officials and Employees Ethics Act (*Ethics Act*) 5 ILCS 430/15-5. See the University of Illinois Office of Business and Financial (OBFS) Services Policies and Procedures, section 9.6, at http://www.obfs.uillinois.edu/manual/central p/sec9-6.html#bb.

B. Allegations of non-compliance should remain confidential to the extent possible. Generally, complainants decide if they wish to remain unidentified or have their identity known. However, in order for a respondent involved in an allegation of non-

compliance to have a meaningful opportunity to be heard, it may be necessary to identify the complainant. If the complainant is a subordinate of the respondent, the Committee will, to the best of its ability, protect the identity of the complainant while conveying the substance of the allegations and information gained to the respondent. The Committee cannot guarantee the anonymity of the complainant.

References:
21 CFR 50.25(b)(5), 21 CFR 56.108(b)(2)
38 CFR 16.103(b)(5)(i), 38 CFR 16.116(b)(5)
45 CFR 46.103(b)(5)(i), 45 CFR 46.116(b)(5)

4.8. Required Educational Training

The COM-R HSPP includes ongoing educational requirements for the research community (*i.e., investigators, department heads, faculty, staff and students*). The HSPP education program consists of initial and continuing mandatory training sessions for all individuals who are engaged in the research, review, or oversight of human subject research at COM-R.

No individual identified as key research personnel on a project will be allowed to conduct research activities involving human subjects without meeting the HSPP training requirements.

A. Key research personnel are engaged in the research and include:
   1. Principal investigators;
   2. Co-investigators;
   3. Individuals listed on the grant or contract application;
   4. Individuals listed on a FDA form 1572 (*for COM-R sites*);
   5. Individuals who are named as contact persons in the informed consent documents or recruitment materials for research;
   6. Individuals who provide supervision of the persons who are obtaining informed consent to participate in research.
   7. Individuals who obtain informed consent or authorization; and
   8. Individuals who have access to PHI.

B. PIs are responsible for the ongoing monitoring of the educational requirements of all research personnel, paying special attention when research personnel are prompted or are given additional responsibilities. A promotion or broadening of duties may trigger new educational requirements from which personnel were previously exempt.

C. Key research personnel are listed on the IRB application and Appendix P and must be reviewed and approved according to their role in the research by the IRB.

D. If students or other individuals are not engaged in the research and are not listed in Section II.A above, then they are not required to be listed on the research protocol. However, the Principal Investigator is responsible to ensure that these individuals receive both adequate training, including human subjects' protection training, and oversight in accordance to the roles these individuals perform in the research.

E. Applications will not be accepted by RSS for IRB review if a PI or faculty sponsor lacks the required human subject protection training. Key research personnel will be excluded from participating in the conduct of the research until they have met the training requirements.

F. Final approval may be withheld if it is determined that an individual, who has not met the HSPP training requirements, is key to the conduct of the research.

G. For further information on who is required to take HSPP training, see COM-R HSPP *Tip Sheet: Human subjects research training requirements*.

4.8.1. Initial Training Requirement:

A. The initial training requirement may be fulfilled by completing the "Basic" on-line Collaborative Initial Training Initiate (CITI) course. If this training has been completed at another institution those credits are transferable. Basic training seminars that have met the equivalent requirements through UIC, OPRS also are accepted on the Rockford campus. All researchers are also required to take the HIPAA for Research training that can be access through the online UIC Training modules of the UIC Vice Chancellor for Research. The training modules that meet this requirement are HIPAA for Research 101, 103, or HSPP 105.

B. RSS should be contacted for other training options available for individuals with limited capacities and lesser roles in the research (*e.g. community liaison*) or for other non-English language options.

C. Educational offerings from other institutions will be evaluated on a case-by-case basis for equivalency to COM-R standards. To submit outside training for approval, submit proof of training along with the course description to RSS.

4.8.2. Continuing Education Requirement:

A. All investigators and other key research personnel involved in human subject research are also required to complete a minimum of two contact hours of COM-R HSPP approved CE in human subject protections every two years.

B. Educational opportunities may be found by attending approved educational offerings on campus (*i.e., RSS, departmental or college programs*) or approved conferences or educational courses dealing with human subject protections within and outside of the institution.

C. Individuals must submit external educational offerings for consideration for HSPP CE credit to OPRS and RSS using the "Requesting Continuing Education Credit" forms available on the OPRS website – http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/forms/index.shtml.

4.8.3. Dissemination of New Information: (*other resources besides 4.7.6. above*).

The following procedure provides the process for keeping IRB members and support staff, investigators, and research staff updated as to new developments, requirements, and policies and procedures related to human subjects research protection.

Resources for Disseminating New Information:

A. IRB Continuing Education. At each of the applicable IRB meetings, IRB members are provided updates on policies, procedures, forms or reviewer checklists by an individual knowledgeable in the subject matter followed by a question and answer session. The UIC OPRS Newsletter and any related materials may be placed on the agenda of applicable Board meetings as part of continuing education. IRB members discuss the applicable newsletter or article at the respective IRB meeting. Articles from external sources may be also used as supplements. Each IRB member receives a copy of the UIC OPRS Newsletters and any related materials to be reviewed at the meeting along with the agenda.

B. Peer review and Trade Publications. From time to time, articles appearing in peer review or trade publications are highlighted by the RSS Specialist and distributed through mass e-mail and/or hard copies.

C. Brown Bag Lunches/Webinars broadcast from the UIC campus. These one-hour sessions may be provided by request to COM-R faculty investigators and research personnel and affiliated community members. Sessions are open to all individuals within a department and to the affiliated community member personnel and may be performed on-site in the Rockford campus or telecast remotely from resources on the UIC main campus. RSS also accepts for credit departmental presentations or lectures if approved by the OVCR prior to the event. The OPRS web site has departmental request forms, as well as individual request forms available on the OPRS website.

D. National Conference Attendance. Credit for national conference attendance can be credited through the OVCR by filling out the form available on the OPRS website. COM-R recognizes the continuing educational credit if approved by the OVCR.

4.9. Developing the Protocol

New researchers are encouraged to review all the information in this section to insure greater understanding of how the details and logistics in data collection, consent, sharing, etc. can impact the level of review concerning a proposed protocol. Full disclosure is required by the COM-R IRB to provide them with the information they need to determine the risk/benefit ratio and make an informed judgment concerning the approval of a protocol and all recruitment and informed consent documents.

4.9.1. Student (*Educational*) Research:

Policies:

A. Research and teaching at COM-R must meet the highest ethical and professional standards.

B. Definitions of research and the strength of the boundary between research and education may vary widely among disciplines. However, normal educational activities, including those designed to train students in research techniques and methods, or to qualify students as researchers, when those activities are conducted as part of courses or in normal classroom settings, often fall outside the federal definition of "research" under 45 CFR 46.102(d) and do not require IRB oversight. For such activities, ethical supervision is provided by the faculty, program directors, department heads/chairs, and college deans.

C. Researchers must consult the appropriate definitions of "research" and "human subject" to determine when they must submit a proposal for review by the IRB. Please use the form *Determination of Whether an Activity Represents Human Subject Research,* which is available on the RSS website and on IRBNet to guide whether the activity is considered to be human subject research. If this form does not prompt the use of an elevated review (*such as Claim of Exemption*) then file this form on IRBNet for a formal Administrative Review. A decision letter will be provided to the P.I. to be kept with for their records as proof that COM-R IRB review is not required.

D. Graduate theses and dissertations are clearly understood as "research" and fall within IRB jurisdiction when "human subjects" (*as defined in 45 CFR 46.102(f)*) are involved.

E. If a student and/or the faculty advisor/class instructor is unsure whether or not the student's project involves human subjects research, they should contact an RSS for advice at (815) 395-5942.

Definitions: "Research Involving Human Subject" means any activity that either:

1) Meets the DHHS definition of "research" and involves "human subjects" as defined by DHHS; or
2) Meets the FDA definition of "research" and involves "human subjects" as defined by FDA.

I. DHHS Definitions:

A. RESEARCH: As defined by DHHS regulations means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (*45 CFR 46.102(d)*).

B. HUMAN SUBJECT: As defined by DHHS regulations means a living individual about whom an investigator (*whether professional or student*) conducting research obtains:
(1) Data through intervention or interaction with the individual, or
(2) Identifiable private information (*45 CFR 46.102(f)*).

C. INTERVENTION: As defined by DHHS regulations means both:
(1) physical procedures by which data are gathered (*for example, venipuncture*) and manipulations of the subject or the subject's environment that are performed for research purposes (45 CFR 46.102(f)), or
(2) communication or interpersonal contact between investigator and subject (45 CFR 46.102(f)).

D. PRIVATE INFORMATION: As defined by DHHS regulations means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and 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*) (*45 CFR 46.102(f)*). "Identifiable information" as defined by DHHS means information that is individually identifiable (*i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information*).

II. FDA Definitions:

A. RESEARCH: As defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior

submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are: synonymous for purposes of FDA regulations (*21 CFR 50.3(c), 21 CFR 56.102(c)*).

(1) "Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act" means any use of a drug other than the use of an approved drug in the course of medical practice (*21 CFR 312.3(b)*).

(2) "Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 5209(g) of the Federal Food, Drug, and Cosmetic Act" means any activity that evaluates the safety or effectiveness of a device (*921 CFR 812.2(a)*).

(3) "Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research (*21 CFR 50.3(c), 21 CFR 56.102(c)*)."

B. HUMAN SUBJECT: As defined by FDA regulations means an individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient (*21 CFR 50.3(g), 21 CFR, 56.102(e)*). A human subject includes an individual on whose specimen a medical device is used.

4.9.1.1. Three Potential Review Categories for Student Research:

A. Student projects that are solely classroom directed exercises and that do not meet the definition of research, and therefore, do not require IRB review (*i.e., activities associated with research methodology courses, field practicum*[1]*, and internships*).

B. Student projects that meet the definition of research under 45 CFR 46.102(d) and that meet the requirements for one or more of the six exemption categories (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm#c) require submission to the IRB/RSS for review and an exemption determination.

C. Student projects that meet the definition of research and that involve human subjects, but do not qualify for an exemption. These projects require review and approval by the IRB. Projects that involve minimal risk and that meet the requirements of one or more of the expedited review categories are eligible for expedited IRB review. (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm#c8). Projects that either do not meet the requirements of the expedited categories or that involve greater than minimal risk require full (*convened*) IRB review.

4.9.1.2. Student Projects That Do Not Require IRB Review:

A. Student projects that have the objective of providing research experience for the student and that do not have the intent or goal to contribute to generalizable knowledge when the project is begun, do not require IRB review or approval. For example, research practica are student projects completed in a course designed to provide students with an opportunity to practice various research methods such as interviews, observations, survey techniques, and sometimes data analysis. These projects are not undertaken to contribute to generalizable knowledge and will not be shared with individuals outside the classroom. Other examples of classroom activities include patient evaluations for nursing students and student counseling techniques.

B. Generally, these projects involve minimal risk to the subjects, and it is highly recommended that the students record data anonymously (*i.e., no names, social security numbers, or codes that can be directly linked to the subject's name*). Frequently, students engaged in learning research techniques conduct research that focuses on controversial or compelling topics. Occasionally, focusing on these sensitive areas, such as collecting data about illegal activities (*i.e., drug abuse, child abuse, prostitution*) can cause emotional distress to subjects or potential risk to the subject if there is a confidentiality breach. Although practica are not under the purview of the IRB, the RSS Specialist is available to provide the student and/or the faculty advisor with guidance regarding protections that could be part of the student research protocol.

   The faculty advisor or instructor should ensure that the research practica are conducted according to current ethical standards for the discipline. All student activities on the Rockford that include surveys, focus groups, and the collection of data about human subjects must have administrative review to insure that the activity has been properly cleared per COM-R policy. The *Determination of Whether an Activity Represents Human Subject Research* form can be found on the RSS website or on IRBNet and submitted to get an administrative review. This formal application will allow the RSS office to provide the student P.I. with a formal decision for their records to verify that the activity has been considered for IRB review.

C. Student projects that meet the definition of research and require an exemption determination by the IRB/RSS or IRB review via expedited or convened review:
   1) Any research that is conducted by students (*graduate, undergraduate*) that will contribute to generalizable knowledge and involves human subjects, must be reviewed by the IRB before the research may begin. This includes students conducting research for their thesis, dissertation, classroom or independent study projects.
   2) Student projects that are exempt from IRB/RSS review include any project that meets the definition of research, includes human subjects, and that meets the criteria for one or more of the exemption categories in the federal regulations.

a. An exemption determination means that the research is exempt from meeting all the research requirements outlined in Subpart A of 45 CFR 46 and would not require continuing IRB review. However, these projects still require that the IRB or RSS make the exemption determination prior to initiation. This determination cannot be made by the researcher. Student projects in this category include projects that might involve interview procedures which collect the data anonymously (*i.e., without the recording of names, social security numbers, or other codes that can be directly linked to the subject*).

b. Examples of research in this category include observations of persons in commonly accepted settings (*provided the researcher does not interact with the subject*), studies that focus on normal educational practices, curriculum, instructional techniques, or management strategies, or studies involving existing data sets or files in which subjects cannot be identified.

c. Please refer to the COM-R RSS form Claim of Exemption application or the Getting Started portion of the RSS web-site for further information regarding the exemption categories and the exemption review process.

3) It is recognized that time constraints accompany projects of this nature, and every effort will be made to review the applications in a timely manner. The student researcher and/or the faculty advisor should plan on submitting a Claim of Exemption application at least two weeks before the research is to begin. Normally, this should allow ample time for the review process to occur. If the project is a requirement for graduation, it is suggested that the applications be submitted very early in the semester in order to allow time for the review process and conduct of the research.

4) All non-exempt student research projects must be submitted for IRB review and approval before the research may begin. For further information regarding the expedited and convened review processes, please refer to the RSS web-site Getting Started page and the Initial Review application forms (*either Biomedical/Health Sciences or Social/Behavioral Sciences, whichever is most appropriate to the research protocol*).

4.9.1.3. Guidelines for Instructors and Faculty Advisors:

A. Even if student projects do not meet the definition of research involving human subjects, it is highly suggested that the research course include basic information about the existence of and the reasons for human subject protection regulations designed to safeguard human research subjects. Students should be familiar with the concepts of ethical conduct of research, risk/benefit analysis, confidentiality, and informed consent, particularly when student research involves the submission of a Claim of Exemption application or an Initial Review application for either expedited

or convened review. It is the instructor's or Faculty Advisor's responsibility to ensure that student research is conducted according to current and applicable ethical standards.

B. Instructors are responsible for screening the individual's student research projects and providing guidance concerning whether it may require IRB administrative review or a determination of exemption. If the student and instructor are uncertain about IRB review and approval or an exemption determination, they should contact the RSS office at (815) 395-5942.

When the research requires IRB review and approval or an exemption determination, it is the instructor's/Faculty Advisor's responsibility to assist the student in preparing the materials to be reviewed by the IRB. If the instructor cannot not fulfill the role of the Faculty Advisor, he/she should assist the student in obtaining an adequate faculty Advisor. The Faculty Advisor is responsible for supervising the student and ensuring that the conduct of the research meets ethical and academic standards, including the adherence to COM-R policies and procedures for human subjects research. The instructor/Faculty Advisor must also maintain the research records for three years after completion of the research, as required by the federal regulations. Depending upon the type of research, longer record retention periods may be required (*i.e., research that involves the use of protected health information*).

C. Before the research protocol application is submitted to the IRB, faculty advisors must ensure that both the student and the Faculty Advisor have completed the required human subjects protection training. If training has not been completed (*both CITI and HIPAA for research*), RSS will not be able to accept the student's application for IRB review. For further information regarding the educational requirements for research investigators, please refer to the RSS web-site: http://tiggeruic.edu/depts/ovcr/research/protocolreview/irb/education/index.shtml.

D. In instances where a class of students will be conducting group or individual research projects of a very similar nature as part of a classroom instruction, and the instructor believes that the research requires IRB review and approval, the instructor may submit a single protocol (*an umbrella protocol*) that covers the research conducted by all the students. All research conducted by the students must fall under the parameters described in the umbrella protocol. Each student should be listed as a co-investigator on the umbrella protocol application to the IRB and meet the necessary human subject protection training requirements.

References:

21 CFR 50.3(c), 21 CFR 56.102(c), 21 CFR 312.3(b), 21 CFR 812.2(a), 21 CFR 50.3(g), 21 CFR 56.102(e)

45 FR 46.102(d), 45 CFR 46.102(f)

4.9.2. Oral History Research:

Within the broader context of social science research, classic history, oral history, biography, and some qualitative interviews do not always meet the definition from the federal regulations of research involving human subjects. Increasingly, however, the application of qualitative research methodologies may render studies that typically would not have required IRB review and approval to be submitted for IRB review or, at least, to require a determination from the IRB as to whether the study is subject to human subjects protection regulations.

According to federal regulations, there are two basic premises upon which the protection of Human research subjects rests: first, that the data gathered from the subjects renders them identifiable, either directly or indirectly. While history, oral history, biography, and some qualitative interviews usually fall squarely within this premise, they typically do not meet the second basic premise of human subjects research (*i.e., the regulatory definition of research*). To meet the regulatory definition of research, data must be gathered and analyzed for the purpose of publishing and/or presenting knowledge that may be generalizable, or can be applied, to a broad segment of the population.

Based upon the narrow specificity – or non-generalizability – of history, oral history, biography, and some qualitative interviews, a substantial segment of historical work would not be considered human subjects research. The federal Office of Human Research Protection (OHRP), having taken current socio-historical practices into consideration, has provided the following guidance to the field in an effort to help distinguish when it may be necessary to submit social science studies involving historical, oral history, biographical, and qualitative interview methodologies to IRB review.

Data-gathering practices that serve to document a specific historical event or the experiences of individuals *without the intent to draw conclusions or generalize findings* would *not* constitute "research" as defined by the federal regulations. One example given is an oral history video recording of interviews with Holocaust survivors where the sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust, and to provide a venue for Holocaust survivors to tell their stories.

The purpose for which the data will be gathered and the methodology(s) applied to the data are key to the determination of whether the study may be subject to human subjects protection regulations. If substantially the same Holocaust survivor data as above were used to draw conclusions, inform policy, or generalize findings, OHRP would consider the study subject to federal regulations and require IRB review. For example, by applying qualitative methodologies to interviews with Holocaust survivors, researchers might analyze how alienation from official Nazi German culture was expressed and draw generalizable conclusions or develop policies regarding the amelioration of sub-group alienation from any "official" or hegemonic cultural standards. The collection of oral histories, biographies, and qualitative interviews for the purpose of creating an archive or repository for future research (*that is, from which future researchers may test hypotheses, draw conclusions, inform policy, or contribute to generalizable knowledge*) is particularly likely to be considered research, thus subject to federal regulations and IRB review.

In keeping with OHRP guidance, the COM-R RSS requires that any research involving humans, including social science studies incorporating historical methodologies, oral history, biographical methodologies, or qualitative interviews, be submitted for a human subjects research determination by the IRB.

4.9.3. Special Protected Populations:

The COM-R IRB ensures that additional safeguards are included in the research design to protect the rights and welfare of research participants who have limited autonomy and are at risk for coercion and undue influence. The Investigator must submit the materials specified in the protocol application for the IRB to obtain information in sufficient detail to make the determinations required by the Federal regulations for approval for conducting the research in the applicable vulnerable population.

The IRB determines whether the research involves participants vulnerable to coercion or undue influence and the required risk categories by reviewing the protocol, IRB application and consent documents to ascertain whether the applicable criteria for approval (*e.g., DHHS, FDA, and/or VA*) are met.

For research in which some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, or persons that are decisionally or cognitively impaired, terminally ill, economically or educationally disadvantaged, the IRB evaluates the research plan to determine whether and to what extent additional safeguards have been included in the study to protect the rights and welfare of these subjects.

For international research or research funded by the Department of Education, Department of Education, Department of Defense, Department of Justice, or the Department of Veteran's Affairs, the IRB follows any additional protections described in the relevant authorities' or agencies' regulations or laws.

4.9.3.1. Children as Research Subjects:

Children are considered by the federal regulations as being vulnerable to coercion. To safeguard their interests and protect them from harm, additional regulatory protections exist for research involving children. The COM-R IRB approves research involving minors only if the research complies with the safeguards described in this policy and procedures.

As stated in its FWA (*Section 2.1.4*.), COM-R has elected to not extend OHRP authority over all human subjects research conducted at COM-R; however, the general protections of the Belmont Report and the Common Rule [*45 CFR 46*] will be applied to all research reviewed and approved at COM-R either in the same way or in a comparable variation. For both federally and non-federally funded research involving children as subjects. The IRB follows federal regulations at 45 CFR 46 Subpart D and 21 CFR 50 Subpart D, in addition to those imposed under COM-R HSPP policies, ethical considerations and other applicable federal, state and local laws for review and approval.

It should be noted that The Department of Education has adopted Subpart D, but the National Science Foundation has not; however, COM-R policy affords the same protections to children

regardless of the funding source and parallels the additional protections afforded to children as codified in Subpart D to all research involving children.

Definitions:

A. ASSENT: a child's affirmative agreement to participate in research. The child's failure to object, absent affirmative agreement, should not be considered assent.

B. CHILD/CHILDREN/MINORS: The federal research regulations define children as individuals who have not attained the legal age for consent to treatments or procedures involved in the research, under the State or local law of the jurisdiction in which the research will be conducted (*45 CFR 46.402(a)*). In Illinois, a minor is defined as an individual under the age of 18 years (*325 ILCS 45/2(c)*) with the exceptions described below. Similarly, child refers to any person less than 18 years of age (*325 ILCS 17*).

C. FOSTER CHILD: In Illinois, a foster child is a ward of the state since the Illinois Department of Children and Family Services, an Illinois state agency, holds guardianship of the person for foster children. (*Juvenile Court Act of 1987, 705 ILCS 405; Children and Family Services Act, 20 ILCS 505*).

D. GUARDIAN: DHHS and the FDA define a guardian as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Illinois, the term Guardian "means a court appointed guardian of the person under legal disability." In Illinois, a variety of guardianship appointments exist and the investigator should take care to document that the guardian's representation of the ward for the research is within the scope of their authority: limited guardianship, plenary guardianship, guardian of the person, guardian of the estate, and temporary guardianship. (Health Care Surrogate Act, 755 ILCS 40; Juvenile Court Act of 1987, 705 ILCS 405/1-2).

E. GUARDIANSHIP OF THE PERSON OF A MINOR: In Illinois, the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having permanent effect on the life and development of the minor and to be concerned with his or her general welfare. It includes but is not necessarily limited to . . . the authority to consent to major medical, psychiatric, and surgical treatment. (Juvenile Court Act of 1987, 705 ILCS 405/1-2). Please contact RSS for guidance in temporary custody situations or for children who are placed by court under the guardianship of a probation officer, as these are complex situations that may require the advice of University Counsel.

F. WARD: A ward means any child who is placed in the legal custody of the state or other agency, institution, or entity, consistent with the applicable federal, state, and local laws and regulations. (*21 CFR 50.3(g)*. In Illinois, a ward of the state includes but is not limited to a child placed by court under the guardianship of the Illinois Department of Children and Family Services. In Illinois, children

placed in foster care are wards of the state. (*Juvenile Court Act of 1987, 705 ILCS 405/2-7*).

4.9.3.2. Circumstances When Minors Can Consent for Themselves:

A. Emancipated or Mature Minor: If a minor has been adjudicated as a "mature minor" or an "emancipated minor"[1] by an Illinois court with jurisdiction over such minor, such minor would also be able to consent to medical treatment and research relating to such treatment under Illinois law. Note that if a minor has only been partially emancipated under the Emancipation of Minors Act, such minor will only have those rights and responsibilities as specified in the court order. When research involves subjects who claim that they are "emancipated" or "mature" minors, the investigator must review and document in the research record the court order that provides such designation before allowing such subject to consent as an adult for the research. An individual aged 17 who is enrolled in the military is also not considered a minor under some circumstances in Illinois.

B. The Illinois Consent by Minors to Medical Procedures Act: (*410 ILCS 210/1*): Illinois law also grants minors the legal capacity to consent to medical treatment in certain situations. The Illinois Consent by Minors to Medical Procedures Act (*410 ILCS 210/1*) permits:

1. A married minor, a minor parent, or a pregnant minor to provide his or her own informed consent to the performance of a medical or surgical procedure performed by:
   (i) a physician licensed to practice medicine and surgery,
   (ii) an advanced practice nurse who has a written collaborative agreement with a collaborating physician that authorizes provision of services for minors, or
   (iii) a physician assistant who has been delegated authority to provide services for minors.

2. A minor parent to provide the informed consent for performance on his or her child of a medical or surgical procedure by a physician licensed to practice medicine and surgery, an advanced practice nurse who has a written collaborative agreement with a collaborating physician that authorizes provision of services for minors, or a physician assistant who has been delegated authority to provide services for minors, or a dental procedure by a licensed dentist.

3. Other instances where the Minors Medical Procedures Act deems a minor to have the same legal capacity to consent as an adult include:
   (i) Emergency treatment of first aid or emergency dental treatment. (410 ILCS 210/3(a)).

   (ii) Medical care or counseling related to the diagnosis or treatment of any disease or injury arising from predatory criminal sexual assault of a child, aggravated criminal sexual assault, criminal sexual assault,

aggravated criminal sexual abuse or criminal abuse of a child. (410 ILCS 210/3(b)).

(iii) Medical care or counseling related to the diagnosis or treatment of a minor 12 years of age or older who may have come into contact with any sexually transmitted disease (STD), or may be determined to be an addict, an alcoholic or an intoxicated person, or who may have a family member who abuses drugs or alcohol. (410 ILCS 210/4).

4. The COM-R IRB extends the provisions of the Minors Medical Treatment Act to research. Specifically, under the circumstances or for the conditions stipulated in the Act, the COM-R IRB views the minor to have the same legal capacity to act and has the same powers and obligations as has a person of legal age to consent for research involving such medical or surgical procedures not covered by the Act. Thus, a 13 year old male seeking medical treatment for alcohol addiction can consent to participate in research involving addiction treatment. The research may not however involve additional activities unrelated to clinical management of the addiction, such as genetic research.

5. A minor who is able to give consent under Illinois State Law is not considered a child under federal regulations.

4.9.3.3. Other Legal and Binding Issues:

A. When assent is required by the IRB, the decision of the child assenting is binding, provided parental or guardian permission, when necessary, has been obtained.

B. When the duration of the children's participation in a research project may continue beyond the age of majority, the investigator must include provisions for obtaining the legally effective from the now adult participants for proceeding with their research participation.

C. A COM-R investigator applying to conduct a research activity involving children in another jurisdiction (*i.e., state*) must become familiar and provide evidence of compliance to the IRB with all applicable legal, professional, and ethical requirements for the conduct of research involving children for each jurisdiction where the research will be conducted.

D. Studies that involve children or other vulnerable populations, are greater than minimal risk and are not conducted in Illinois must be reviewed and approved by an IRB in the appropriate jurisdiction (*i.e., state*) as well as the COM-R IRB.

4.9.3.4. IRB Responsibilities:

A. As part of their determination, based upon risk and benefit, the IRB must consider additional safeguards that are appropriate to the subject population, classify research involving children into one of four categories, document its discussions of the risks and benefits of the research study, and make appropriate determinations as to permission from the parent or guardian and assent from the child.

B. When reviewing research involving children, the IRB chair will ensure that at least one member with experience in research involving children is present at the meeting. If necessary expertise is not available among the members, the services of an ad hoc consultant with appropriate experience will be sought.

C. For FDA-regulated research, the COM-R IRB reviews the proposal research in accordance with 21 CFR 50 Subpart D.

4.9.3.5. Categories of Research Involving Children:

For these categories, minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (*45 CFR 46.102*). Please review Table I below for detailed information as to approval criteria be category. The second column details what the IRB must find and document protocol specific information in review guides for expedited review or meeting minutes for convened review.

Table I: Approval Criteria for Categories of Research Involving Children.

Category 1: Research Not Involving Greater than Minimal Risk (45 CFR 46.404; 21 CFR 50.51)	
1. The research presents no more than minimal risk to the children; and 2. Adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians as set forth at 46.408.	Permission of one parent is permitted if approved by the IRB.
Category 2: Research Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Child (45 CFR 46.405; CFR 50.52)	
1. The research presents more than minimal risk to the children by an intervention or procedure that holds out the prospect of direct benefit for the individual child, or by a monitoring procedure that is likely to contribute to the child's well-being; 2. The risk is justified by the anticipated benefit to the child; 3. The relation of the anticipated benefit to the risk is at least as favorable to the children as that presented by available alternative approaches; and 4. Adequate provisions are made for obtaining the assent of the child and permission of their parents or legal guardians as set forth at 46.408.	Permission of one parent is permitted if approved by the IRB.

Category 3: Research Involving Greater than Minimal Risk and No Prospect of Direct Benefit to the Individual Child, but Likely to Yield Generalizable Knowledge about the Child's Disorder or Condition. (45 CFR 46.406; 21 CFR 50.53).	
1. Greater than minimal risk is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual child, or by a monitoring procedure which is not likely to contribute to the well-being of the child; 2. Risk represents a minor increase over minimal risk; 3. Intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; 4. Intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and 5. Adequate provisions are made for soliciting assent of the children and permission of their parents or legal guardians.	Permission of both parents is required unless: 1. One parent is deceased, unknown, incompetent, not reasonably available, or 2. Only one parent has legal responsibility for care and custody of child.
Category 4: Research Not Otherwise Approvable, which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children 945 CFR 46.407 and 21 CFR 50.54).	
For research where the IRB finds the research does not meet the requirements set forth in categories 46.404, 46.405 or 46.406 as described above in this table, the IRB may approve the research only if: 1. The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and 2. If Federally funded or under the purview of the FDA, the Secretary of DHHS or, if applicable, FDA Commissioner, after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment, has determined either: A. That the research in fact satisfies the	Permission of both parents is required unless: 1. One parent is deceased, unknown, incompetent, not reasonably available, or 2. Only one parent has legal responsibility for care and custody of the child. For research that is not federally funded or under the purview of the FDA, and the IRB determines such research falls within category 46.407, the COM-R IRB will provide copies of the protocol and the IRB minutes to the HPA for a determination regarding whether an ad hoc panel of experts should be convened to review the research in a process parallel to that

conditions of categories 46.404, 46.405, or 46.406; or B. The following: 1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; 2. The research will be conducted in accordance with sound ethical principles; and 3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.	of OHRP expert panel review. In this case, COM-R IRB approval will not be released until either the HPA determines an ad hoc panel is not necessary or the ad hoc panel issues a recommendation that the research is acceptable.

4.9.3.6. Requirements for Obtaining Assent from Children:

A. The IRB must find that adequate provisions are made for soliciting the assent of children when in the judgment of the IRB the children are capable of providing assent.

B. The IRB in judging whether children are capable of assenting must take into account the ages, maturity, and psychological state of the children involved.

C. When the IRB determines that assent of a child is required, it shall also determine whether and how assent must be documented.

D. The IRB may make the judgment concerning capability to assent either for all children or just some of the children to be involved in the research.

E. The COM-R IRB generally requires assent from children ages seven years and older, unless the IRB finds their capability to provide assent is compromised. However, the IRB may at their discretion extend this requirement to children younger than 7 years for certain types of research.

F. The assent should provide the child with an explanation of the proposed research procedures and an understanding of what is being requested of them in a format (*i.e., oral and/or written*) and language that is appropriate to the child's age, experience, maturity, and condition.

G. For children between 7 to 12 years of age, the assent should be limited to one page and focus on describing what participation in the research will entail, such as what activities will occur, how long it will take, and whether it may involve any pain or discomfort. The use of illustrations or diagrams is encouraged with this age group. The assent is generally presented orally to the child with a written document (*i.e., script of presentation*) available for the child to document their assent.

H. For children older than 12 years of age, an assent written in age-appropriate language and containing the same elements as in an adult consent form should be provided. In fact, older children, e.g., 16 or 17 years of age, due to their higher maturity and cognitive ability may be able to read, understand, and subsequently sign the adult consent document.

I. The investigator must describe the procedures to be used for soliciting assent in COM-R RSS form *Appendix B*.

4.9.3.7. Waiver of Assent:

A. The assent of a child is not a necessary condition for proceeding with the research (*i.e., it may be waived*) if the IRB determines and provides protocol specific information documenting that:
   1. The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
   2. The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.

B. Even where the IRB approves a waiver of assent, it is generally desirable to still provide the child with an understanding of the research. The IRB may require the investigator to prepare an "information sheet" that provides the child with an explanation of the study in a format (*oral and/or written*) and language appropriate for the child's age, experience, maturity and condition.
   1. A decision by the IRB that the children are capable of assenting does not prevent the IRB from waiving assent under the conditions for which consent may be waived at 45 CFR 46.116(d)(1-4):
      a. The research involves no more than minimal risk to the subject;
      b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
      c. The research could not practicably be carried out without the waiver or alteration; and
      d. Whenever appropriate, subjects will be provided with additional pertinent information after participation.

4.9.3.8. Provisions for Obtaining Permission from Parents or Legal Guardians:

A. The IRB must find that adequate provisions are made for soliciting the permission of each child's parents (*or guardians*).

B. The permission form provided parents or guardians must contain the basic elements of consent as stated in 45 CFR 46.116(a) (1-8) and 21 CFR 50.25(a)(1-8) and any additional elements the IRB deems necessary.

C. Permission by parents or guardians must be documented in the same manner as required for informed consent of subjects.

D. The investigator must describe the procedures to be used for obtaining parental or guardian permission in COM-R form *Appendix B*.

4.9.3.9. Waiver of Parent or Guardian Permission:

The IRB may waive the requirement for obtaining permission from parents or guardians when:

A. The research does not fall under FDA regulations, and

B. The research either:

1. Meets the provisions for waiver in 45 CFR 46.116(d)(1-4), see above, **or**

2. The IRB determines that the research is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (*for example, neglected or abused children*).

3. When the requirement for parental or guardian permission is waived according to above, an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted. Also, the waiver must not be inconsistent with federal, state or local law. Selection of an appropriate mechanism is guided by the nature and purpose of the research activities, the risk and anticipated benefit to the subjects, and their age, maturity, status, and condition.

4.9.3.10. Investigator Responsibilities:

A. Investigators are responsible for determining any changes in the Legally Authorized Representative (LAR) status for children participating in research for all cases with vulnerable populations.

B. The investigator must be particularly attentive with wards, since the LAR may change if the ward is adopted or if the parents
regain guardianship.

C. The investigator must perform one of the following at minimum:

1. Periodically assess with an adult accompanying the child if there has been a change in guardianship;

2. Including a statement in the informed consent form that the guardian should inform the investigator when there is a change in the guardian status; **and**

3. Any other methods to ensure prompt notification of a change in guardianship status.

4.9.3.11. Wards:

A. For research conducted with wards in Illinois, the COM-R IRB must receive documentation of Illinois Department of Children and Family Services (DCFS) approval for wards of this department prior to approving any research involving DCFS wards.

B. For foster children, the COM-R IRB must also follow the specific foster agency requirements concerning the appointment of an advocate as provided by the investigator.

C. Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 or 46.407 only if such research is:

1. Related to their status as wards; **or**
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

D. If the research is approved under 45 CFR 46.406 or 46.407, the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or *in loco parentis*. One individual may serve as advocate for more than one child. The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (*except in the role as advocate or member of the IRB*) with the research, the investigator(s), or the guardian organization.

E. Illinois DCFS Criteria for Approval of Research Involving Children.

1. Investigators contemplating a request that the COM-R IRB review whether wards may be included to the population cohort of a research protocol should note that DCFS has different definitions for terms used in the Common Rule [*45 CFR 46*] to afford greater protections to wards. For example: The DCFS definition of "Maximum Allowable Risk" means "the greatest possible risk [DCFS] will permit to the children and families it serves. This risk must not be greater overall than would normally encountered in the daily lives or in the routine medical or psychological care or examination of a comparable group of Illinois children for whom [DCFS] is not legally responsible. Since abused, neglected, dependent and other children for whom [DCFS] is legally responsible and their families may already by psychologically or physically disadvantaged compared to the general population of children or families, minimal risk requirements for these children and families will be more stringent than for the general population" (*89 ILADC 432*).

2. The DCFS "Research Review Board" must first approve the research before the COM-R IRB can review the research. Investigators should note that documentation of approval form DCFS is required prior to submission to the COM-R IRB. Please allow sufficient time for DCFS to process this submission.

3. The DCFS "Research Review Board" "will receive, review and analyze all proposed research which would involve children and families served by [DCFS], or records of such children and families, and research proposed by [DCFS] providers." (*89 ILADC 432*).

4. The criteria by which proposed research will be evaluated by DCFS:
    a. Offers minimal risk to children and families served by [DCFS];
    b. Assures that the safest procedures are used consistent with sound research design and methodology;
    c. Makes adequate provision to protect the privacy rights of children and families and to maintain confidentiality of records;
    d. Maintains human dignity;
    e. Shows promise of producing, confirming or otherwise advancing knowledge of child or family emotional or physical conditions;
    f. Assures that subjects will be selected in an equitable manner consistent with the goals of the research whenever appropriate;
    g. Assures that adults, older children and infants have been considered in that order for participation in the proposed research whenever appropriate; AND
    h. Assures that, when feasible, the research will be used for diagnostic and treatment purposes to directly benefit participating subjects. (89 ILADC 432).
    i. In addition, the following two criteria will also be used in the evaluation:
        (1) The time and inconvenience requested of children and families participating in research and the extra workload that may be borne by [DCFS] staff must be justified by the expected benefits derived from the research, and the soundness of the research design.
        (2) Selection of children and families who may participate in research will not be based solely on administrative convenience, availability of populations living in conditions of social or economic deprivation, or convenient access to the population. (89 ILADC 432)

5. The Illinois Administrative Code provides "no experimental use of a drug may be made, and no drug of an experimental nature may be given or administered in any form or manner to any minor under the care of the [DCFS], except when this department has the power to consent to major medical treatment and procedures and when, in the opinion of the treating physician and of at least two medical experts not professional associated with the recommending physician, the administration of an experimental drug would represent the best possible change of saving the minor's life or achieving the remission of a progressive, crippling, disfiguring, or potentially fatal disease. This provision is at all times subject to court review." (89 ILADC 432)

F. Investigator Responsibilities.

1. Investigators should note, however, the restrictions and additional protections required for subjects who are wards when considering the initial research design. COM-R RSS recommends that individuals who would like to enroll wards contact COM-R RSS staff for guidance. COM-R RSS also recommends that investigators who are not anticipating a large cohort of the study population to be wards to first submit the protocol for approval without including the ward population. Once the underlying research is approved by the IRB, then the investigator should submit an amendment to add the ward population.
2. The investigator has a responsibility to disclose whether he or she believes that wards of the state could be recruited after approval is granted as part of the application process.
3. Investigators have an ongoing responsibility to immediately notify the IRB and RSS and submit an amendment when an enrolled subject becomes a ward of the state while the research is active.
4. Investigators have a responsibility to be familiar with the specific requirements of foster agencies as to research with DCFS wards.

G. IRB Responsibilities.

1. The IRB needs to follow the recommendations of the foster agency as to the appointment of an advocate if the foster agency requires the appointment of an advocate regardless of risk.
2. The IRB has the responsibility to make protocol-specific findings as to the ward of the state regulatory criteria, which COM-R RSS staff has a responsibility to document in the meeting minutes.

References:

45 CFR 46 Subpart D; 21 CFR 50 Subpart D
21 CFR 50.51, 21 CFR 50.52, 21 CFR 50.53, 21 CFR 50.54, 21 CFR 50.25(a)(1-8)
45 CFR 46.116(d)(1-4), 45 CFR 46.404. 45 CFR 46.405; 45 XDR 46.406; 45 CFR 46.407, 45 XDE 46.116(a)(1-8)
VHA Handbook 1200.05
325 ILCS 45/2(c), 325 ILCS 17
Wards Permanency Advocacy Services, 89 ILADC 327.5
Research Involving Children and Families , 89 ILADC 432
Juvenile Court Act of 1987, 705 ILCS 405/1-2

4.9.4. Pregnant Women/Fetuses:

Pregnant women represent a vulnerable population when involved in human subjects' research and require additional safeguards from the investigator and IRB, because of women's additional safeguards from the investigator and IRB, because of women's additional health concerns during pregnancy and

the need to avoid unnecessary risk to the fetus. The IRB must apply additional federal and state regulations and laws. To safeguard their interests and protect them from harm, additional regulatory protections exist for research involving pregnant women, human fetuses and neonates. The COM-R IRB approves research involving these vulnerable groups only if the research complies with the safeguards described in this policy and 45 CFR 46 Subpart B.

The COM-R IRB reviews and considers research involving pregnant women, human fetuses, and neonates of uncertain viability or nonviable neonates in accordance with the federal regulations at 45 CFR 46 Subpart B, COM-R HSPP policies and procedures, and other applicable federal, state and local laws.

The COM-R IRB also considers the need for additional safeguards when reviewing research in which women of childbearing potential are possible subjects as the potential exists for these women to become pregnant during the course of the research.

Definitions: (*The following definitions are taken from 45 CFR 46.202.*)

A. DEAD FETUS: A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

B. DELIVERY: Complete separation of the fetus from the woman by expulsion or extraction or any other means.

C. FETUS: The product of conception from implantation until delivery.

D. NEONATE: A newborn.

E. NONVIABLE NEONATE: A neonate after delivery that, although living, is not viable.

F. PREGNANCY: The period of time from implantation until delivery. A woman is assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

G. VIABLE: As it pertains to the neonate, means being able, after delivery, to survive (*given the benefit of available medical therapy*) to the point of independently maintaining heartbeat and respiration.

4.9.4.1. The Illinois Consent by Minors to Medical Procedures Act (*410 ILCS 210/1*):

The Illinois Consent by Minors to Medical Procedures Act (*410 ILCS 210/1*) permits a pregnant minor to provide her own informed consent to the performance of a medical or surgical procedure performed by:

(i) a physician licensed to practice medicine and surgery,

(ii) an advanced practice nurse who has a written collaborative agreement with a collaborating physician that authorizes provision of services for minors, or

(iii) a physician assistant who has been delegated authority to provide services for minors.

The COM-R IRB extends the provisions of the Minors Medical Treatment Act to research. Specifically, under the circumstances or for the conditions stipulated in the Act, the COM-R IRB views the minor to have the same legal capacity to act and as having the same powers

and obligations as a person of legal age to consent for research involving such medical or surgical procedures. The minor is not deemed to be able to provide consent for research involving conditions not stipulated by the Act or involving medical or surgical procedures not covered by the Act. In these instances, assent from the pregnant minor and permission from the parent or guardian must be obtained as described in the COM-R HSPP policy and procedure *Research Involving Children*.

4.9.4.2. Studies in Which Pregnancy is Coincidental to Subject Selection:

When the research population may include women of child bearing potential, the possibility exists for the inadvertent inclusion of pregnant women. For these studies, the IRB will consider:

A. Whether it is appropriate to provide a statement as part of the informed consent process that the particular treatment or procedure may involve risks to the subject (*or to the embryo, fetus or nursing infant*) that are unforeseeable;

B. Whether the mother's participation would pose any risk to the fetus or nursing infant;

C. Whether there is a need to ensure that nonpregnant subjects are advised to avoid pregnancy or nursing for a time during or following the research;

D. Whether there is a need for the investigator to advise the subject to immediately contact the investigator should they become pregnant; and

E. Whether the potential risk is sufficient to justify requiring either excluding pregnant women from the research or requiring specified methods of contraception during and following participation in the research.

4.9.4.3. Research Involving Pregnant Women or Fetuses:

The two primary considerations of the IRB in evaluating research involving pregnant women or fetuses are:

(1) Whether the research is directed to the mother's or fetus' health, and

(2) The risk to the woman and fetus.

Pregnant women or fetuses may be involved in research if the IRB determines and documents in a protocol specific manner in the meeting minutes or review guide (*as appropriate*) that all of the following conditions are met:

A. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses (*45 CFR 46.204(a)*);

B. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus: or if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means; and

C. No inducements, monetary or otherwise, will be offered to terminate a pregnancy; and

D. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

E. Individuals engaged in the research will have no part in determining the viability of a neonate; and

F. Any risk is the least possible for achieving the objectives of the research.

G. Consent of the pregnant woman solely is obtained in accord with the informed consent provisions of 45 CFR 46 Subpart A when the research holds out:

(1) The prospect of a direct benefit to the pregnant woman,

(2) The prospect of direct benefit both to the pregnant woman and the fetus, or

(3) No prospect of benefit for the woman or the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important medical knowledge which cannot be obtained by any other means.

H. Consent of the pregnant woman and father is obtained in accord with the informed consent provisions of 45 CFR 46 Subpart A when the research holds out prospect of direct benefit solely to the fetus, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest; and

(1) Each individual providing consent as stated above, is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(2) For pregnant women under 18 years of age, consent may be obtained from the minor subject when the research relates to expected medical or surgical procedures performed in pregnant women by the individuals and under the circumstances stipulated in the Illinois Consent by Minors to Medical Procedures Act (*410 ILCS 210/1*). When the research does not fall within the Act, assent from the pregnant minor and permission from the patient or guardian must be obtained as described in the COM-R HSPP policy and procedure *Research Involving Children.*

4.9.4.4. Research Involving Neonates:

A. Neonates of uncertain viability and nonviable neonates may be involved in research if ALL of the following conditions are met:

(1) Where scientifically appropriate, pre-clinical and clinical studies have been conducted and provide data for assessing potential risks to neonates; **and**

(2) Each individual providing consent is fully informed regarding the reasonable foreseeable impact of the research on the neonate; **and**

(3) Individuals engaged in the research will have no part in determining the viability of the neonate; **and**

(4) The requirements of paragraph B or C of this section (*refer below*) have been met as applicable.

B. Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this policy unless the following additional conditions have been met:

(1) The IRB must determine that:

a. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; **or**

b. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; **and**

c. The legally effective informed consent of either parent of the neonate, or if neither parent is able to consent of either parent of the neonate, or if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with 45 CFR 46 Subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

C. Nonviable neonates. After delivery, a nonviable neonate may not be involved in research covered by this policy unless ALL of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained; **and**

(2) The research will not terminate the heartbeat or respiration of the neonate; **and**

(3) There will be no added risk to the neonate resulting from the research; **and**

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means; **and**

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with 45 CFR 46Subpart A, except that the waiver and alteration provisions of 46.116(c) and (d) do not apply; however, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph.

D. Viable Neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of 45 CFR 46 Subparts A and D.

4.9.4.5. Post Delivery, Placenta, Dead Fetus, or Fetal Material:

A. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissues, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and

regulations regarding such activities, which may include the Illinois Anatomical Gift Act (*755 ILCS 50*).

B. If information associated with material described in paragraph A of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research participants and all pertinent subparts of the regulations are applicable.

4.9.4.6. Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Fetuses or Neonates.

For research which is not federally funded and the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates and the research is not approvable under the above provisions (s*ections II and III*), the IRB will provide copies of the protocol and the IRB minutes to the HPA for a determination regarding whether an *ad hoc* panel of experts should be convened to review the research. In this case, COM-R IRB approval will not be released until either the HPA determines that an ad hoc panel is not necessary or the *ad hoc* panel issues a recommendation that the research is acceptable based on either:

1. That the research in fact satisfies the conditions above, as applicable; **or**
2. The following:
   (a) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

   (b) The research will be conducted in accord with sound ethical principles; and

   (c) Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

3. Research which is federally funded and meets the conditions described in **4.6.3.3.4.** (*above*) must be sent to the Secretary of Health and Human Services for review and approval. The secretary will determine the approvability based on the criteria stated in 45 CFR 46.207(b).

4.9.4.7. Modification or Waiver of Specific Requirements:

Upon the request of the investigator (*with the approval of the IRB*), the Secretary of the Department of Health and Human Services may modify or waive any of the above requirements of federal law but not requirements of State law.

References:

45 CFR 46.202, 45 CFR 46.116(c)-(d), 45 CFR 46 Subparts A and D,
45 CFR 46 subpart B, 45 CFR 46.202
The Illinois Anatomical Gift Act, 755 ILCS 50
The Illinois Consent by Minors to Medical Procedures Act, 410 ILCS 210/1

4.9.5. Decisionally and Cognitive Impaired as Research Subjects:

It is the policy of the COM-R IRB to review, approve, and provide guidance as to ethical considerations to afford additional protections when cognitively and decisionally impaired subjects are involved in human subjects research to uphold their rights and welfare and to prevent coercion or undue influence.

Definitions:

A. COGNITIVELY IMPAIRE: Having either a psychiatric disorder (*e.g., psychosis, neurosis, personality or behavior disorders*), an organic impairment (e.g., dementia) or a developmental disorder (*e.g., mental retardation*) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests. (*Penslar RL, Porter JP, Institutional Review Board Guidebook, Chapter 6: Special Classes of Subjects, OHRP, 1993*).

B. COMPETENCE: Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (*or not acting*) on that information, and to make a choice. (*See terms Incompetence, Incapacity*) Competence may fluctuate as a function of the natural course of a mental illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically. As a designation of legal status, competence or incompetence pertains to an adjudication in court proceedings that a person's abilities are so diminished that his or her decisions or actions (*e.g., writing a will*) should have no legal effect. Such adjudications are often determined by inability to manage business or monetary affairs and do not necessarily reflect a person's ability to function in other situations. (*Penslar RL, Porter JP, Institutional Review Board Guidebook, Chapter 6: Special Classes of Subjects, OHRP, 1993*).

C. CLOSE FRIEND: In Illinois, "Any person 18 years of age or older who has exhibited special care and concern for the patient and who presents an affidavit to the attending physician stating that he or she:

(i) is a close friend of the patient,
(ii) is willing and able to become involved in the patient's health care, and
(iii) has maintained such regular contact with the patient as to be familiar with the patient's activities, health, and religious and moral beliefs. The affidavit must also state facts and circumstances that demonstrate that familiarity."

(755 ILCS 40/10).

D. DECISIONAL CAPACITY: In Illinois, "the ability to understand and appreciate the nature and consequences of a decision regarding medical treatment or foregoing life-sustaining treatment and the ability to reach and communicate an informed decision in the matter as determined by the attending physician." (*755 ILCS 40/10*).

E. GUARDIAN: DHHS and the FDA define a guardian as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Illinois, the term Guardian "means a court appointed guardian of the person who serves as a representative of a minor or as a representative of a person under legal disability." In Illinois, a variety of guardianship appointments exist and the investigator should take care to document that the guardian's representation of the ward is within the scope of their authority: limited guardianship, plenary guardianship, guardian of the person, guardian of the estate, and temporary guardianship. (*Health Care Surrogate Act, 755 ILCS 40*).

F. INCAPACITY: Refers to a person's mental status and means inability to understand information presented to appreciate the consequences of acting (*or not acting*) on that information, and to make a choice. Often used as a synonym for incompetence. (*Penslar RL, Porter JP. Institutional Review Board Guidebook, Chapter 6: Special Classes of Subjects, OHRP, 1993*).

G. INCOMPETENT: A legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

H. LEGALLY AUTHORIZED REPRESENTATIVE (LAR): DHHS and the FDA define a legally authorized representative as "an individual or judicial or other body authorized representative as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." (*46.102(c); 21 CFR 50.3*).

Policy:

COM-R policy is guided by OHRP's *Institutional Review Board Guidebook* (*Chapter 6 Section D*), i.e., "the predominant ethical concern in research involving individuals with psychiatric, cognitive, or developmental disorders [*including temporary or sporadic decisional impairment resulting from substance abuse or trauma*] is that their disorders may compromise their capacity to understand the information presented and their ability to make a reasoned decision about participation. Many individuals with disabilities affecting their reasoning powers may be residents of institutions responsible for their total care and treatment. The impact of institutionalization may further compromise their ability to exercise free choice (*voluntariness*). (*These concerns apply both to voluntary patients and those committed involuntarily*.)."

This policy and procedure is based on the following Illinois state laws: the Illinois Health Care surrogate Act (*755 ILCS 40/1 et seq*.), the Mental Health Treatment Preference Declaration Act (*755 ILCS 43/10*), and the Medical Practice Act (*410 ILCS 50/3.1*). These statutes, other than the Medical Practice Act, relate to medical treatment decisions; however, the COM-R HSPP has extended application of the concepts of these statutes to research. RSS and IRB members consult with the Office of University Counsel when needed. PIs should contact RSS with any questions concerning Illinois state law or this policy.

4.9.5.1. IRB Requirements for Approval:

A. The IRB must include a member knowledgeable about and experienced with the mentally disabled or cognitively impaired (*Refer to COM-R HSPP Identification and Use of Ad Hoc Consultants policy*).

B. The IRB must consider the following points, as adopted from OHRP's *Institutional Review Board Guidebook* (*Chapter 6 Section D*), in its review of protocols involving cognitively or decisionally impaired subjects. The findings may be documented either in a review guide or meeting minutes:

1. The IRB should be aware of any applicable Illinois state law, particularly those relating to consent by family members on behalf of persons incapable of consenting on their own. Note that consent to participation in research may differ from consent to medical treatment. In addition, it should be noted that some federal agencies (*including components of the Department of Defense*) prohibit the participation of mentally disabled persons in research conducted under their auspices (*Adapted from OHRP Guidance on Special Classes of Subjects*). Refer to COM-R HSPP policy *Informed Consent Process and Informed Consent Documents*. RSS staff may refer additional questions to the UIC Office of University Counsel.

2. Research involving cognitively or decisionally impaired subjects should be relevant to the subject's condition or circumstances. There must be a compelling justification for including the decisionally or cognitively impaired as subjects. Decisionally or cognitively impaired individuals must NOT be subjects only because they were available.

3. If the investigator proposed to recruit institutionalized individuals who are decisionally impaired, justification for using that population must be provided. For example, are non-institutionalized subjects appropriate for the research and reasonably available? Further, does the research pertain to aspects of institutionalization?

4. The PI must propose adequate procedures for evaluating the mental status of prospective subjects to determine whether they are capable of consenting. Determination of capacity to consent or inability to withdraw may be made through a standardized measure and/or consultation with another qualified professional in accordance with the level of risk and the prospect of benefit. The PI must explain and the IRB must determine whether these procedures are appropriate both to the subject population and the nature of the proposed research.

5. If more than minimal risk is involved in the research, the IRB must determine whether the risk is justified by the anticipated benefits to the participating subjects and the importance of the knowledge that may reasonably be expected to result.

6. In reviewing a protocol, the IRB must evaluate:
    a. How persons authorized to give legally valid consent on behalf of any individuals lacking the capacity to consent will be identified;
    b. Whether assent of prospective subjects should be required; and
    c. Whether objections to participation by subjects who lack the capacity to give valid consent can be overridden and, if so, under what circumstances can this occur.
7. The IRB must evaluate whether:
    a. An advocate or consent auditor should be appointed to ensure that the preferences of potential subjects are elicited and respected; and
    b. An individual should be designated to ensure the continuing agreement of subjects to participate as the research progresses.
8. The IRB must evaluate whether:
    a. The patient's physician or other health care provider must be consulted before any individual is invited to participate in the research;
    b. The research is likely to interfere with ongoing therapy or regimens; and
    c. The request to participate itself might provoke anxiety, stress, or other serious negative response.
9. The IRB should ensure that:
    a. Procedures have been devised to ensure that the subject's LAR is well informed regarding his or her role and obligations to protect the subject,
    b. LARS are given descriptions of the studies; and
    c. Informed that their obligation is to try to determine what the subject would do if competent.

4.9.5.2. Record Retention:

The PI should obtain and keep all legal records related to authority to consent, including advance directives, court orders, guardianship documentation, and applicable documentation as to wards of the state.

4.9.5.3. Informed Consent Process:

Care must be taken to insure that the informed consent process is adhered to and documented. Please refer to the specific details provided below.

4.9.5.4. General Principles:

A. In most cases, for subjects who have been determined to lack decision making capacity, the consent of the subject's Legally Authorized Representative LAR is required and assent should be obtained from the subject.

In research where there is potential for direct benefit to the subject, the IRB may waive the requirement to obtain assent; however, consent from the (LAR) must be obtained, except where the FDA exemptions for one-time emergency use or emergency research are met.

B. In order to seek consent from a LAR, the PI must obtain a copy of the documents certifying that the subject is unable to make decisions; a copy of the advance directives or other applicable document, if applicable; the court order, if applicable; or any other evidence that the person believed to be the LAR has this authority.

C. Informed consent for subjects determined to lack the capacity to provide consent should be obtained from a LAR. Because neither the Medical Patient Rights Act nor the Health Care Surrogate Act provides definitive statutory authority for surrogate consent in research studies, the HSPP has developed the following priority list for surrogates, incorporating the stipulations from these two statutes and the Mental Health Treatment Preference Declaration Act:

1. Individuals authorized to act on behalf of the subject in the event they are incapacitated in an operable and unrevoked living will under the Illinois Living Will Act, an operable and unrevoked declaration for mental health treatment under the Mental Health Treatment Preferences Declaration Act, or an authorized agent under a power of attorney for health care under the Illinois Power of Attorney Act when the patient's condition falls within the coverage of the living will, the declaration for mental health treatment, or the power of attorney for health care.
2. Subjects' guardian of the person;
3. The subject's spouse;
4. Any adult son or daughter of the subject;
5. Either parent of the subject;
6. Any adult brother or sister of the subject;
7. Any adult grandchild of the subject;
8. A close friend of the subject;
9. The subject's guardian of the estate.

4.9.5.5. Informed Consent Process: Fluctuating Capacity.

A. Since capacity to consent or the ability to withdraw may fluctuate, the IRB must evaluate the process for continued verification of understanding and willingness to participate by the subject.

1. The consent procedures should describe a plan for protecting individuals who may lose their capacity to provide consent or their

ability to withdraw while participating in research activities (*such as an advocate or an ombudsman*).

2. If a LAR provides initial consent to the research and during the research the subject is determined to be capable of providing informed consent, the PI must obtain consent from the subject.

3. The IRB may require an outside witness observe and confirm the consenting process.

4. The IRB may request the PI to obtain from the subject a valid advance directive in instances where incapacity of the subject may be expected to occur during the period of study conduct, either as a result of the research or expected progression of the subject's condition.

4.9.5.6. Risk and Benefit Considerations:

A. The IRB must find that appropriate provisions in accordance with the level of risk and the prospect of benefit are made for determining the subject's ability to provide consent or their ability to withdraw, such as the following:
   1. The ability to make a choice;
   2. The ability to understand relevant information;
   3. The ability to appreciate the situation and its likely consequences; and
   4. The ability to think through information rationally.

B. The research should not impose a risk of harm, unless the research is intended to benefit the subject and the probability is greater than the probability of harm.

C. The IRB must consider the items below in making the determination of whether an independent assessor is required to determine the level of decisional incapacity of the subject:
   1. No more than minimal risk;
      a. The IRB may allow PIs to make the determination as to the ability of the subject to consent.

   2. Greater than minimal risk – and direct benefit:
      a. The IRB may require an independent assessment or expert to make the determination as to the ability of the subject to consent.

      b. The independent assessor must be qualified both by educational attainment and professional experience in his or her field in a manner appropriate to the proposed subject population.

   3. a. The IRB must require an independent assessment by an expert to make the determination as to whether the subject is competent to consent.

b. The independent assessor must be qualified both by educational attainment and professional experience in his or her field in a manner appropriate to the proposed subject population.
c. The IRB must determine that the research would be highly valuable to the general field of study when the research is greater than minimal risk and does not offer direct benefit.

4. The IRB must consider the degree of ability of the potential subject, the level of risk, and the prospect of benefit to the individual subject.

4.9.5.7. Diminished Capacity and VA Research:

A. Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. The IRB includes at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.

2. Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.

3. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

4. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents (*appointed under Durable Power of Attorney for Health Care (DPAHC)*) and next-of-kin, or guardians must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if

competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

B. The IRB must make a determination in writing of each of the criteria listed above. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives as defined below.

C. Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.

D. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

E. Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (*surrogate consent*).

1. Such consent may be obtained from: a health care agent appointed by the person in a DPAHC or similar document; court-appointed guardians of the person, or from next-of-kin in the following order of priority, unless otherwise specified by applicable state law: spouse, adult child (*18 years or older*), parent, adult sibling (*18 years of age or older*), grandparent, or adult grandchild (*18 years of age or older*).

2. Such consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements or as established by a legal determination.

   a. The practitioner, in consultation with the chief of service, or COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

   b. Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.

   c. Disclosures required by VHA Handbook 1200.05 to be made to the subject by the investigator must be made to the subject's surrogate.

d. If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

References:
21 CFR 50.3
45 CFR 46.102(c)
Illinois Living Will Act
Illinois Health Care Surrogate Act (*755 ILCS 40/1 et seq.*)
Medical Practice Act (*410 ILCS 50/3.1*)
Mental Health Treatment Preferences Declaration Act (*755 ILCS 43/10*)

4.9.6. VA Research: Human Biological Specimens (*Collected, Used, and/or Stored From Veterans For Research*):

NOTE: All research conducted at the Jesse Brown VA MUST go through UIC OPRS. Any other VA research can go through the COM-R IRB if the PI is affiliated with COM-R.

The PI must outline the procedures for specimen collection in the application form and provide applicable information for each type of human biological specimen that will be collected. Human biological specimens collected as part of a research protocol are not considered "banked specimens" if the specimens are used for the specific objectives outlined in the approved research protocol and are then destroyed when the analysis is complete or at the termination of the research project. Specimens collected and stored for future research purposes that are not specified in the original research protocol are considered "banked specimens." Included in this category are specimens and their related biomaterials (*i.e., DNA*) that are collected under a particular research protocol, but reused for a different protocol. The banked specimens collected during a VA research protocol must be banked at either a VA sponsored or a VA approved tissue bank.

If the specimens are sent to a non-VA institution for testing as defined in the protocol, once the specific analyses are performed, the remainder of the specimens must be destroyed or returned to the VA for destruction. If the specimens are destroyed at another institution, that institution must certify the destruction of the specimens in writing.

4.9.6.1. Timeline:

A. If the protocol is 5 years or longer and the specimens are stored off-site at a non-profit institution until the end of the protocol, then the investigator must obtain a waiver from ORD.

B. If the specimens are stored off-site at a non-academic, for-profit institution for greater than 3 months while awaiting analysis, a waiver must be obtained from ORD.

4.9.6.2. When Banked Specimens are Obtained:

If banked specimens are obtained, the PI must provide the following information in addition to the informed consent elements detailed in COM-R HSPP policy and procedure *Required and Additional Informed Consent Elements for VA Research*, if applicable to the study, and must incorporate the following information in the Informed Consent Document:

A. The types of specimens stored and the name and location of the biorepository/tissue bank where the tissues will be stored;

B. The types of future research that the sample will be used for. When applicable, list types of research for which the specimens will be used (*e.g., any research*); research conducted by the Investigator only; research conducted by other investigators; research related to specific diseases. COM-R RSS recommends the use of check boxes that can be checked within the informed consent form;

C. If the specimen will be shared with other researchers for approved research protocols;

D. The length of time the specimen will be stored;

E. Will the specimens be stored without any identifiers (de-identified) or coded (*linked*)? If coded, how coding will occur, where will code sheet be stored or who will have access to code? Will the research results be conveyed to the participant and/or health care provider?

(1) **Example 1**: The sample and your clinical data will be assigned a code that does not contain your name, initials, SSN, date of birth, or other unique identifiers.

(2) **Example 2**: All identifiable information about you will be removed from the research specimen. Your sample and data will be identified by a code.

F. When and under what conditions will research results be conveyed to the subject, the subject's family or the subject's physician? In other words, will the human subject be contacted after the completion of the original research?

G. The steps necessary for the subject to withdraw from the study and any future studies in which the specimens may be used. The consent must indicate what will occur to the data collected to that point and that the specimen and the code that links the subject's clinical data to the specimen will be destroyed;

H. Disclose any potential commercial benefits and if the subject will receive money or other benefits. For example, will the specimens be used to generate cell lines?

I. Disclose any intent to perform genetic tests.

J. Disclose any potential risks to the subject or the subject's family. Potential risks may include breach of confidentiality, which may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to the subject or the subject's family.

4.9.6.3. For Banked and Non-banked Specimens:

If specimens are sent to a non-VA institution for analysis, such analysis should be outlined in the original research protocol. A written understanding between the VA PI and the non-VA institution must specify the analysis to be performed outside the VA. When not approved for sample banking, the remainder of the specimens must be returned to the original VA PI for destruction. Alternatively, the remainder of the specimens and related biomaterials may be destroyed at the non-VA institution on condition that the institution certifies in writing that the specimens have been destroyed.

4.9.6.4. COM-R IRB Control of Data:

All clinical and personal data associated with the human biological specimens collected as part of research projects conducted by the VA PI at VA facilities or approved off-site locations must be maintained under COM-R IRB control, whenever possible. When this is not possible, the minimal amount of clinical data should be shared with individuals conducting statistical and other analysis.

4.9.6.5. National Cancer Institute (NCI) and Other Comparable Sponsored Tissue Banks:

VA investigators using the National Cancer Institute (NCI) and other comparable sponsored tissue banks do not need to submit a request for a VA approved tissue bank to ORD. These sponsored tissue banks are designated a general waiver as "VA approved" tissue banks.

When a repository is designated as a "VA approved" tissue bank, VA investigators can use the designated repository for banking human biological specimens collected under the COM-R IRB approved protocols for VA Research without submitting a request to ORD. See the references below for a list of the most current VA approved tissue banks.

References:

VA FAQ: *Banking of Human Biological Specimens for Research*
List of VA Approved Tissue Banks, available at:
http://www.research.va.gov/programs/tissuebanking/ApprovedTissueBanks.pdf
VA Document: Informed Consent for Protocols Involving Tissue Banking
VHA Handbook 1200.05 Appendix C
VA Form: Application for an Off-Site Tissue Banking Waiver

4.9.6.6. General Requirements for Informed Consent (Cited from VHA Handbook 1200.05, Appendix C):

An investigator may not involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the person or the person's legally authorized representative. If someone other than the investigator conducts the interview and obtains consent from a patient, the investigator needs to formally delegate this responsibility , and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study.

NOTE: *This policy does not apply to research ruled exempt from Institutional Review Board (IRB) review. (Refer to COM-R HSPP policy and procedure Exempt Review of Research and VHA Handbook 1200.05, Appendix A).*

1. An investigator must seek such consent only under circumstances that:
    a. Provide the prospective subject or the subject's legally-authorized representative sufficient opportunity to consider whether or not to participate, and
    b. Minimize the possibility of coercion or undue influence.
2. The information that is given to the subject or the subject's representative must be in language understandable to the subject or the subject's representative.
3. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears from liability for negligence.
4. VA Form 10-1086, Research Consent Form, or an electronic version of VA Form 10-1086, must be used as the consent form, and all required elements must be completed.

4.9.6.7. Basic Elements for Informed Consent:

In seeking informed consent, the following information must be provided to each subject:

1. Name of the study
2. The name of the Principal Investigator (PI)
3. A statement that the study involves research
4. An explanation of the purposes of the research and the expected duration of the subject's participation
5. A description of the procedures to be followed and identification of those being done for research purposes

6. Identification of any procedures that are experimental
7. A description of any reasonably foreseeable risks or discomforts to the subject including for example, privacy risks (*legal, employment, and social*)
8. A description of any benefits to the subject, or to others, which may reasonably be expected from the research
9. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
10. A statement describing the extent to which confidentiality of records identifying the subject will be maintained. If appropriate, a statement that Federal agencies such as the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP) and the Government Accounting Office (GAO) may have access to the records. If an FDA-regulated test article is involved, the FDA requires a statement that the FDA may choose to inspect research records that include the subject's individual medical records.
11. For research involving more than minimal risk an explanation as to whether any compensation is available and an explanation as to whether any medical treatments are available if injury occurs and if so, what they consists of, or where further information may be obtained.
    a. According to Title 38 Code of Federal Regulations (CFR) 17.85 "Treatment of Research-Related Injuries to Human Subjects," VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Except in limited circumstances, the necessary care must be provided in VA medical facilities. Exceptions include: situations where VA facilities are not capable of furnishing economical care; situations where VA facilities are not capable of furnishing the care or services required; and situations involving a non-veteran research subject. Under these circumstances, Directors may contract for such care. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. The informed consent form needs to include language explaining VA's authority to provide medical treatment to research subjects injured by participation in a VA research project. ***NOTE:*** *VA regulations on research related injuries (see 38 CFR 17.85 apply to minimal-risk research*.
    b. The regulation at 38 CFR 17.85 does not apply to research conducted for VA under a contract with an individual or a non-VA institution (although veterans injured as a result of participation in

such research may nevertheless be eligible for care from VA under other statutory and regulatory provisions). Information on the responsibility for research-related injury under such circumstances must be included in the consent form. ***NOTE:*** *It is strongly suggested that the investigator make provisions for coverage of such cost in research awards and contracts.*

12. An explanation of whom to contact for answers to questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject. At least one contact's name and phone number must be other than the investigator's or study personnel.
13. A statement that participation is voluntary, and that refusal to participate will involve no penalty or less of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
14. A statement that a veteran-subject will not be required to pay for care received as a subject in a VA research project except as follows:
    a. In accordance with Title 38 United States Code (U.S.C.) 1710(f) and 1710(g) certain veterans are required to pay co-payments for medical care and services provided by VA. Veterans receiving medical care and services from VA that are not rendered as part of the VA-approved research study, must pay any applicable co-payment for such care and services.
    b. Suggested wording for the consent form needs to note this requirement. For example: "Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payments requirements will continue to apply medical care and services provided by VA that are not part of this study."
    c. Investigators need to note, pursuant to 38 CFR 17.102, charges will not be made for medical services, including transportation furnished as part of a VA-approved research study. Section 17.102 requires that if services are furnished to a person who is not eligible for the services as a veteran, the medical care appropriation will be reimbursed from the research appropriation.

4.9.6.8. Additional Elements of Informed Consent:

One or more of the following elements of information must also be provided to each subject when appropriate:

A. A statement that the particular treatment or procedure may involve currently unforeseeable risks to the subject, or to the embryo or fetus, if the subject is or becomes pregnant.

B. Anticipated circumstances under which the subject's participation may be term-

inated by the investigator without the subject's consent.

C. Any additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment.

D. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

E. A statement that significant new findings developed during the course of the research which may relate to this subject's willingness to continue participation will be provided to the subject.

F. The approximate number of subjects involved in the study.

G. If the investigators believe that the human biologic specimens obtained could be part of, or lead to, the development of a commercially valuable product, or if the specimens are to be retained after the end of the study, current VA policy and Veterans Health Administration (VHA) regulations must be followed. **NOTE:** If genetic testing is to be done, VA requirements pertaining to

genetic testing must also be met.

H. As appropriate, a statement regarding any payment the subject is to receive and how payment will be made.

4.9.6.9. Defined: 38 CFR 16.116(c):

A. Approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or

B. Waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payments for benefits or services under those programs.
2. The research could not practicably be carried out without the waive or alteration.
3. As defined in 38 CFR 16.116(d), an IRB may:
    a. Approve a consent procedure that does not include, or that alters,

some or all of the elements of informed consent set forth in this appendix; or

b. Waive the requirements to obtain informed consent, provided the IRB finds and documents that;

c. The research involves no more than minimal tangible or intangible risk to the subjects;

d. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

e. The research could not practicably be carried out without the waiver or alteration; and

f. Whenever appropriate, the subjects must be provided with additional pertinent information after participation.

4. The informed consent requirements stated are not intended to pre-empt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

***NOTE**: Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.*

4.9.6.10. Documentation of the Informed Consent:

A. Except as provided in subparagraph 3d of this appendix, informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by:
   1. The subject or the subject's legally-authorized representative.
   2. A witness whose role is to witness the subject's or the subject's legally-authorized representative's signature, and
   3. The person obtaining the informed consent.

B. **VA Form 10-1086**, or an electronic version of VA Form 10-1086, must be used as the consent form. If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the subject's signature; if the same person needs to serve both capacities then a note to that effect must be placed under the witness's signature line.
   1. The consent form must be the most recent IRB-approved consent form. The approval must be documented by the use of a stamp or preprinted box on each page of the consent form that indicates the date of the most recent IRB approval of the form. The IRB must maintain a copy of the approved form in its records.

2. The original signed consent form must be filed in the subject's case history.

3. A copy of the signed informed consent must be provided to the subject or the subject's legal representative.

C. **Consent Form.** Except as provided in subparagraph 3f of this document, the consent form may be either of the following:

1. **Written Consent Document**. VA Form 10-1086 (*either paper or electronic version*), must be used as the consent form and must embody the elements required by this appendix and 38 CFR 16.116. In addition, it must contain any additional elements as required by the IRB. The consent form may be read to the subject or the subject's legally-authorized representative. The investigator must ensure that the subject (*or representative*) is given adequate opportunity to read the form and ask questions before signing it.

2. **Written Consent Document (Short Form**). A shortened written consent document stating that the elements of informed consent required by this appendix and 38 CFR 16.116 have been presented orally to the subject or the subject's Legally Authorized Representative (LAR). When this method is used, there must be a witness to the oral presentation. This process includes the following:

a. The IRB must approve a written summary of what is to be said to the subject or the subject's legally-authorized representative.

b. Only the short form is to be signed by the subject or the subject's LAR.

c. The witness must sign both the short form and a copy of the summary. The person actually obtaining the consent must sign a copy of the summary. The original short form and summary must be filed, as required.

d. A copy of the summary must be given to the subject or the subject's LAR, in addition to a copy of the signed short form.

3. **Progress Note**. A progress note documenting the informed consent process must be placed in the subject's medical record.

a. At a minimum, the progress note must include:

(1) The name of the study,

(2) The person obtaining the subject's consent,

(3) A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process,

(4) A statement that the study was explained to the subject, and

(5) A statement that the subject was given the opportunity to ask questions.

b. An entry must also be placed in the progress note when the human subject is actually entered into the study and when the human subject's participation is terminated. ***NOTE:*** *Consent and entry notes can be combined when both occur at the same visit.*

D. **Waiver of Requirement for a Signed Informed Consent.**

1. An IRB may waive the requirement for the investigator to obtain a signed consent for some or all subjects, if it finds either:
   a. That the only record linking the subject and the research would be the consent document and the principal risk to the subject would be potential harm resulting from a breach of confidentiality. Each subject must be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
   b. That the research presents no more than minimal risk of harm to subject's and involves no procedures for which written consent is normally required outside of the research context.
2. In cases in which the documentation requirement is waived, the IRB must document the reason for the waiver and may require the investigator to provide subjects with a written statement regarding the research.

References:
VHA Handbook 1200.05, Appendix C

4.9.7. Prisoners as Research Subjects:

Potential research subjects who are prisoners are at increased risk for coercion and undue influence as a result of their incarceration. To ensure their participation in research is uncoerced and voluntary, additional protections are afforded this population. Only COM-R IRBs that meet composition requirements in Procedure Section III of this document are permitted to review protocols involving prisoners as subjects. The applicable COM-R IRBs approve research involving prisoners only if the research complies with the safeguards described in this policy. This policy applies whether the research involves individuals who are prisoners at the time of enrollment in the research, who become prisoners after they are enrolled in the research, or whether the research targets prisoners as subjects or their involvement is incidental to the research.

Definitions: (*The following definitions are taken from 45 CFR 46.303*)

A. PRISONER: any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment

procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. Common examples fitting the regulatory definition of prisoner include:

1. Individuals in any kind of penal institution, such as a prison, jail or juvenile offender facility whose ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
2. Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration are prisoners; however, individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community are not prisoners.
3. Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration are prisoners; however, individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to nonpenal institutions for treatment because their illness makes them a danger to themselves or others, are not prisoners.
4. Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.
5. Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. Institutions may consult with OHRP when questions arise about research involving these populations.

B. MINIMAL RISK: the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. **Note:** This definition of minimal risk differs from that in 45 CFR 46 Subpart A by replacing "harm or discomfort" with "physical or psychological harm" and using "healthy person" as the reference point for the medical, dental or psychological examinations.

4.9.7.1. COM-R Follows 45 CFR 46 Subpart C:

For research involving prisoners as participants, the COM-R IRB follows federal regulations at 45 CFR 46 Subpart C in addition to those imposed under other COM-R HSPP policies and procedures, ethical considerations and other applicable federal, state and local laws for review and approval. The exemptions from IRB review at 45 CFR 46.101(b) DO NOT apply to research involving prisoners.

4.9.7.2. Prohibited Prisoner Research:

Medical, cosmetic, or pharmaceutical experiments involving prisoners are prohibited for research to be conducted within the Illinois Department of Corrections. (*Title 20 Corrections,*

Criminal Justice, and Law Enforcement Chapter 1: Department of Corrections: part 106, Research and Evaluation). Therefore, even though these types of research with prisoners may be approvable under federal regulations, they are not permitted under Illinois state law.

4.9.7.3. Review Requirements for Prisoner Research:

COM-R policy generally requires that the review of research involving prisoners be performed by the convened IRB. The exception is protocols originally approved by the convened IRB and remaining active only for data analysis may be eligible for expedited review. (*Refer to COM-R HSPP policy and procedure Expedited Review for Initial and Convened Review and Amendments)*.

4.9.7.4. Special Protections for Research Involving Prisoners (*Documentation*):

When the IRB is reviewing a protocol in which a prisoner is a subject, the IRB must make (*and document in the meeting minutes in a protocol specific manner*) the following seven findings (*45 CFR 46.305(a)*) for approval:

A. The research under review represents one of the following categories of research permissible under 45 CFR 46.306(a)(2) and listed in section II. below;

B. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prisoner is impaired;

C. The risks involved in the research are commensurate with the risks that would be accepted by non-prisoner volunteers;

D. Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

E. The information is presented in language which is understandable to the participant population;

F. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

G. Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

4.9.7.5. Categories of Research Involving Prisoners:

When reviewing a protocol involving prisoners as subjects, the IRB must determine and document whether the study falls within one of the categories allowed for prisoner participation: (*45 CFR 46.306(a); June 20, 2003, DHHS Secretarial Waiver*).

A. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;

B. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;

C. Research on conditions particularly affecting prisoners as a class (*e.g., vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults*) provided that the study may proceed only after the Secretary of DHHS has consulted with appropriate experts including experts in penology, medicine, and ethics and published notice, in the *Federal Register*, of the Secretary's intent to approve such research; or

D. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health and well-being of the participant. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary of DHHS has consulted with appropriate experts including experts in the division of criminology that deals with the philosophy and practice of society in its efforts to deter criminal activities, medicine, and ethics and published notice, in the *Federal Register*, of the Secretary's intent to approve such research.

E. In 2003, a fifth category of permissible research was added by DHHS Secretarial Waiver for Certain Epidemiologic Research. The criteria for this category are that the research must have as its sole purpose:

(i) To describe the prevalence and incidence of a disease by identifying all cases, **or**

(ii) To study potential risk factor associations for a disease.

Also, COM-R must certify to the OHRP that the IRB found the research to fulfill criteria B – G in Procedure Section 4.11.2.4. (*above*) (*45 CFR 46.305(a)(2)-(7)*) and find and document that the research presents no more than minimal risk, no more than inconvenience to the prisoner-subjects, and prisoners are not a particular focus of the research.

4.9.7.6. Composition of the IRB when Prisoners are Involved in Research:

A. When the IRB reviews a protocol involving prisoners as participants, the composition of the IRB must satisfy the following requirements of HHS regulations at 45 CFR 46.304 (a) and (b):

1. A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB; and

2. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB only one IRB need satisfy this requirement.

B. In the absence of choosing someone who is or has been a prisoner, the IRB should choose as a prisoner representative a person with a close working knowledge, understanding and appreciation of prison conditions from the prospective of a prisoner. Suitable individuals could include prison chaplains, prison psychologists, prison social workers, other prison service providers, or persons who have conducted advocacy for the rights of prisoners. The IRB must meet the special composition requirements for all types of review of protocols, including initial review, continuing review, review of protocol modifications, review of reports of adverse events or unanticipated problems involving risk to participants or others, or in the event an individual becomes a prisoner while participating in a research protocol.

C. The IRB must notify OHRP of any change in the IRB roster due to the addition of a prisoner representative. Specifically, the IRB should:

1. Notify OHRP of the name and qualifications of the prisoner representative, if the approved IRB roster does not currently reflect this information; and

2. Maintain the CV of the prisoner representative serving on the IRB.

4.9.7.7. When a Current Research Subject Becomes a Prisoner:

A. If a subject becomes a prisoner, or the discovery of subjects with prisoner status as incidental to the research, after enrolling in a research study which was not approved for prisoner participation, the investigator is responsible for reporting the event in writing to the IRB using the *Prompt Reporting to the IRB* form within 10 working days.

B. If the study was not previously reviewed and approved by the IRB in accordance with the requirements of Subpart C, all research interactions and interventions with, and the obtaining of identifiable private information must cease until the requirements of Subpart C are satisfied. This is necessary because it is unlikely that review of the research and the informed consent document contemplated the constraints imposed by the possible future incarceration of the participant. ***NOTE:*** *The IRB Chair may determine that the participant may continue to participate in the research until the requirements of Subpart C are satisfied when the investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated. The investigator should submit this request using the COM-R RSS Protocol Exception form.*

C. If the investigator would like to have the participant continue in the research, an amendment requesting prisoner review and Appendix C should be submitted to the

RSS. The convened IRB reviews the application for prisoner review and protocol, taking into consideration the additional ethical and regulatory concerns for prisoners involved in research.

4.9.7.8. Research Conducted or Supported by DHHS:

A. For research involving prisoners that is conducted or supported by HHS, COM-R must certify to the DHHS Secretary (*through OHRP*) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46 Subpart C and made the seven additional findings required under 45 CFR 46.305. The COM-R IO or designee sends to OHRP a letter certifying the above and including the name and address of the institution and identity of the research protocol and any relevant HHS grant application or protocol. COM-R also submits:

1. Copy of the research proposal, including IRB-approved protocol, any relevant HHS-grant application, any IRB application forms, and any other information requested or required by the IRB to be considered during initial IRB review;
2. OHRP FWA number;
3. IRB registration number for designated IRB; and
4. Date(s) of IRB meeting(s) in which protocol was considered, including brief chronology that encompasses the date of initial IRB review and date of Subpart C review, if different.
5. All prisoner research certification letters should be mailed to: OHRP Prisoner Research Coordinator, Office for Human Research Protections (OHRP), The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.

B. The Secretary (*through OHRP*) must determine that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2) and give approval prior to the initiation of research activities.

4.9.7.9. Research That is Not HHS Funded or Conducted:

A. If an investigator engages in non-HHS supported research involving prisoners, certification to DHHS (OHRP) is not required.

B. If the IRB deems the research involving prisoners to fall within categories C or the appropriate portion of D, the COM-R IRB will provide copies of the protocol and the IRB minutes to the HPA for a determination regarding whether an *ad hoc* panel of experts should be convened to review the research in a process parallel to that of OHRP expert panel review. In this case, COM-R IRB approval will not be released until either the Human Subject's Protection Administrator (HPA) determines an ad hoc panel is not necessary or the ad hoc panel issues a recommendation that the research is acceptable.

4.9.7.10. Additional Approvals:

A. The Federal Bureau of Prisons places special restrictions on research that takes place within the Bureau of Prisons under 28 CFR 512. The provisions under 28 CFR 512 specify additional requirements for prospective researchers (*both employees and nonemployees*) to obtain approval to conduct research within the Bureau of Prisons and responsibilities of Bureau of Prisons staff in processing proposals and monitoring research projects.

B. Illinois department of Corrections research involving prisoners or access to inmate records in Illinois must comply with the applicable requirements. For research involving prisoners within the Illinois Department of Corrections (IDOC), approval of the Director of IDOC is required.

4.9.7.11. Additional Considerations:

When a prisoner is under 18 (*e.g., an adolescent in a juvenile detention facility is a prisoner*), the HSPP and COM-R IRB policies and procedures regarding children and minors in research also apply.

4.9.7.12. Investigator Responsibilities:

A. Investigators are responsible for obtaining and providing documentation of approval from the detention or correctional facility involved (*i.e., prisons, jails, workhouses, etc.*) to the IRB.

B. Investigators must provide any additional documents or materials required for certification to the Secretary (*through OHRP*) for federally funded research involving prisoners.

C. Investigators may not screen, recruit, or enroll any individual involuntarily confined or detained in a penal institution without written IRB approval. If the biomedical or behavioral research is conducted or supported by HHS, it also requires review and written approval by the Secretary (*through OHRP*) before any research activities may begin, including screening and enrollment.

D. If the investigator anticipates that some of the subjects may become prisoners during the study, submission for prospective IRB review for research involving prisoners should occur.

4.9.7.13. Additional VA Requirements for Prisoner Research:

Research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the VA Chief Research & Development Officer (CRADO). If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (*refer to 45 CFR Part 46, Subpart C 46.301-46.306*).

References:

28 CFR 512

45 CFR 46.303, 45 CFR 4.101(b), 45 CFR Part 46, Subpart C 46.301-46.306, 45 CFR 46.304(a) and (b)

VHA Handbook 1200.05
The Illinois Department of Corrections: Title 20 Corrections, Criminal Justice, and Law Enforcement, Chapter 1: Department of Corrections: part 106, Research and Evaluation.

4.9.8. International Research:

A. If a foreign institution or site is engaged in research:

1. The COM-R IRB reviews all human subjects international research to ensure that adequate procedures are in place to protect the rights and welfare of the subjects.

2. For FDA regulated trials, non-IND studies must follow Good Clinical Practice guidelines rather than the Declaration of Helsinki.

3. The COM-R IRB may approve the research if "the procedures prescribed by the foreign institution affords protections that are at least equivalent to those provided in 45 CFR 46." (*45 CFR 46.101(h)).*

4. The COM-R IRB must approve each research study before research can begin at the foreign institution or site. The foreign institution or site must obtain local IRB/IEC review and approval (*or appropriate equivalent*) for each research study being added to the research. The investigator must submit an amendment to the COM-R RSS adding the foreign institution or site and provide a copy of the foreign institution approval and/or review before the COM-R IRB can approve the study for conduct at the foreign institution or site as a performance site.

5. If the necessary cultural expertise is not on the COM-R IRB, the COM-R IRB may utilize an *ad hoc* consultant in accordance with COM-R HSPP policy "*Identification and Use of Ad Hoc Consultants*."

6. The COM-RRSS may consult with OHRP to ensure equivalent protections are in place, including the identification of an equivalent IRB/IEC for the site.

B. If the foreign institution or site is not engaged in research. (*Refer to "Determining Whether a Performance Site or an Institution is Engaged or Not in Research" for more information as to the "engaged or not" determination*).:

1. If the foreign institution or site has an IRB/IEC, the investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/ IEC or provide documentation that the site's IRB/IEC has determined that approval is not necessary for the PI to conduct the proposed research at the site.

2. When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained detailing that the institutional or oversight officials are allowing the research to be conducted at the performance site.

3. The COM-R IRB must receive documentation of the foreign institution or site's IRB/ IEC determination, or letter of cooperation (*as applicable*), prior to the approval of the research.

4. The investigator and the foreign institution or site is responsible for ensuring that the resources and facilities are appropriate for the research.

5. If the necessary cultural expertise is not on the Board, the COM-R IRB may utilize an ad hoc consultant in accordance with the COM-R HSPP policy "*Identification and Use of Ad Hoc Consultants*.".

C. The COM-R IRB considers local research context when reviewing international studies. In most cases, the COM-R IRB relies on the review of the foreign institution or site's IRB/IEC to assess local research context issues and to assess whether the PI is providing adequate protections in place to protect the rights and welfare of the participants.

D. The informed consent documents must be in a language that is understandable to the potential subjects. The investigator must provide a written translation of the exact content of the foreign language informed consent document, as well as the credentials of the translator. The COM-R IRB reviews the informed consent documents.

4.9.8.1. Monitoring of Approved International Research:

A. The COM-R IRB may require:
   1. Documentation of regular correspondence between the PI and the foreign institution or site;
   2. Documentation of continuing IRB/IEC approval from the foreign institution or site;
   3. Documentation of continuing cooperation from the foreign institution or site if the institution or site is not engaged in the research;
   4. Documentation from other sources than the PI that there have not been any substantial changes in the research since the last continuing review; and/or
   5. The inclusion of an independent monitor/body as part of the data safety monitoring plan.

References:

45 CFR 46.101(h)

FDA Final Rule

VHA Directive 2005-050, "Requirements for Conducting VA-Approved International Research Involving Human Subjects, Human Biological Specimens, or Human Data." Nov. 4, 2005

4.9.9. Local Research Context:

If the COM-R IRB becomes the IRB of Record for a protocol that raises a local research context issue, the IRB must demonstrate that it has obtained sufficient information, and will be able to maintain sufficient oversight, regarding the local research context in the following instances:

A. When the COM-R IRB is geographically removed from the site(s) at which the research will be conducted; and/or

B. When the research involves a distinct participant population with respect to elements including, but not limited to, primary language and/or culture, subculture, ethnicity, and/or religion. (*Refer to COM-R HSPP tip sheet Involvement of Non-English Speaking Subjects in Research for additional information*).

The COM-R IRB must review the adequacy of local research context at initial review as well as at each subsequent continuing review and when applicable amendments are submitted for both minimal risk and greater than minimal risk research studies.

The COM-R PI applying to conduct a research activity in another jurisdiction must first become familiar, and provide evidence of compliance, with all applicable legal, professional, and ethical requirements of each jurisdiction where the research will be conducted. National, state, and local requirements may be implicated.

The COM-R PI is responsible for promptly reporting any changes in the local research context that may influence or alter the risk/benefit analysis for both minimal risk and greater than minimal risk research studies.

Studies that involve vulnerable populations and are greater than minimal risk that are not conducted in Illinois must be reviewed and approved by an IRB in the appropriate jurisdiction, as well as the COM-R IRB.

References:
OHRP Guidance: IRB Knowledge of Local Research Context, dated July 21, 2000

4.9.9.1. Involvement of Non-English Speaking Subjects in Research

The inability to understand spoken English or read and comprehend documents written in English prevents a subject from actively taking part in the consent process and from making an informed decision about participation. Investigators need to be aware of the difficulties inherent in providing accurate and effective consent to non-English speaking individuals and ensure appropriate safe-guards are in place to protect the rights and welfare of these individuals.

The principle of Justice as embodied in the Belmont report (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) calls for *". . . fair procedures and outcomes in the selection of research subjects."* The COM-R IRB implements this principle for non-English speaking subjects by requiring COM-R investigators:

- To provide an ethical and scientific justification for excluding subjects who cannot understand or read English, but otherwise are eligible to participate, from a research proposal.
- To include non-English speaking subjects in research, particularly when the research offers the subject the potential for direct benefit, unless the COM-R IRB reviews and approves the investigator's justification for exclusion.

4.9.9.1.1. Obtaining and Documenting Informed ConsentL

The federal regulations (45 CFR 46.116 and 21 CFR 50.20) require that informed consent information be presented to a research subject *"… in language that is understandable to the subject (or authorized representative)"* and, except in infrequent situations, be documented in writing. Subjects who are not English-speaking should be provided with a translation of the consent document in a language understandable to them. The federal regulations (45 CFR 46.117 and 21 CFR 50.27) permit two methods by which this requirement can e fulfilled:

(1) A written consent document translated into a language understandable to the subject or their Legally Authorized Representative (LAR) (*e.g., foreign language translation of the IRB approved English informed consent form)* or

(2) A "short form" written consent document stating that the elements of consent have been presented orally to the subject or LAR.

The IRB determines which procedure is appropriate for documenting informed consent on a protocol specific basis.

The process of obtaining and documenting informed consent of subjects who do not speak English at COM-R is also impacted by Illinois state law. Statute 110 ILCS 305/20 of the University of Illinois Act states that, if a person is to participate as a subject in a research experiment conducted at the College of Medicine but does not understand the English language, then the informed consent document for the research experiment must be written in a language that the person does understand. If the person cannot read or has difficulty reading, the document must be read to the person in that same language.

As a result of this statute, a complete written translation of the English consent document (*with a testament to the literal translation from the translator*) or a short form and oral translation may be acceptable.

Method 1: Written Translation of IRB-Approved English Informed Consent

- ✓ The COM-R IRB requires a written translation of the full English consent document into a language understandable by potential subjects when:
  - ➢ The research targets a specific population that is non-English speaking;
  - ➢ A significant proportion of subjects are anticipated to be non-English speaking; or
  - ➢ The research is to be conducted at the College of Medicine.
- ✓ Translations of the informed consent documents must be reviewed and approved by the IRB.
- ✓ It is recommended to first obtain approval for the English version of the consent in other languages as an amendment.

- ✓ A back-translation of the consent document(s) to check for accuracy should be carried out. Whenever possible, the back translation should be performed by another qualified individual. ***Note:*** *Depending on the scope, complexity and risk-benefit of the research, the IRB may require an independent back-translation.*
- ✓ The subject, if agreeing to participate, and member of research team obtaining consent must sign and date the IRB-approved foreign language version of the consent document. If a translator fluent in English and the subject's language should be available to address the subject's questions and assess their comprehension.
- ✓ The consent process, including the language used and presence of translators or witnesses, should be appropriately documented in the research record (*i.e., source document*) and, if applicable, medical record.
- ✓ The following items should be submitted for IRB review and approval of the foreign language translation of the full consent document:
  - ➢ IRB-approved English language informed consent document;
  - ➢ Consent document translated into the desired language;
  - ➢ Endorsement from translator that a back translation of the consent into English was performed and was found to be accurate;
  - ➢ Documentation of the translator's qualifications (*i.e., expertise in the foreign language, such as certified translator, native speaker or other evidence of* fluency, and an appropriate scientific or medical background); and
  - ➢ Plan to ensure an adequate consent process and how communication will be facilitated during the research.

Method 2: Short Form Consent Process

- ✓ The COM-R IRB may approve the use of an oral presentation along with a "short form" consent document in a language understandable to the subject when:
  - ➢ The research does not target a non-English speaking population, and
  - ➢ Only a small proportion of subjects are anticipated to be non-English speaking.
  - ➢ The short form is a document written in language understandable to the subject stating that the elements of informed consent, which are outlined on the form in general terms, have been presented orally and understood by the subject (*or their legally authorized representative*).
  - ➢ Templates for the short form in English and several foreign languages are provided on the RSS form website for investigators to download

and use. The translator assisting with the consent process should fill in the protocol specific information where indicated by the blank lines on the form.

- COM-R IRB approval of the foreign language short form consent document and process is required, even when using the RSS downloadable templates. To avoid delay in subject enrollment or incurrence of a protocol violation, investigators are urged to anticipate the presentation and language requirements of potential non-English speaking subjects.

- Requirements for obtaining informed consent when using a short form consent document:

✓ A summary of the informed consent information for the research is presented orally in a language understandable to the subject (*or their authorized representative*). Typically, the IRB-approved English consent form is used for this purpose (*this is the IRB recommended approach*).

- The subject is provided a copy of the short form written in the language the subject is fluent in to review.

- A translator fluent in the subject's language and English must read the consent summary (*i.e., IRB approved English consent form*) to the subject (*or their authorized representative*) in their language. The translator should also be available to address the subject's questions and assess their comprehension. The translator may be a member of the research team.

- A witness to the oral presentation fluent in the subject's language and English is required to attest to the adequacy of the consent process and to the subject's voluntary consent. The translator may also serve this role, if they are not a member of the research team.

✓ Requirements for documenting the consent process when using the short form:

- The subject (*of their authorized representa*tive) must sign and date the short form written in the appropriate language, if agreeing to participate.

- The witness must sign and date the foreign language short form and a written copy of the orally presented consent information (*i.e., typically the IRB approved English consent form*).
- The research team member obtaining consent must sign and date a written copy of the orally presented consent information.
- A copy of the signed short form in the subject's language and the orally presented consent information must be given to the subject (*or their authorized representative*).

- The consent process, including the language used and presence of translators or witnesses, should be appropriately documented in the source document and, if applicable, medical record.

✓ The following items should be submitted for IRB review and approval of the short form consent process:

- Justification for the short form process;
- English and foreign language versions of the short form (*if the short form is NOT from the COM-R RSS website, the source of the form and credentials of the translator should be described*);
- Written summary (*in English*) of the consent information to be presented orally (*the IRB-approved English language consent is recommended to be used for this purpose*); and
- Plan to ensure an adequate consent process and how communication will be facilitated during the research.

4.9.9.2. Additional Considerations - Informed Consent Process and Research Procedures:

Informed consent is a process that requires investigators to continuously re-assess the subject's understanding of the nature of the research, its risks and benefits. Adequate communication between the research staff and subject must occur throughout the research to ensure the safety and welfare of the subject and the integrity of the research data. The IRB submission should discuss the recruitment, consent and continuing participation of non-English speaking subjects in the research. In addition to the consent documents, the investigator must submit for IRB review and approval any recruitment materials that have been translated. The investigator is expected to translate and submit to the IRB any study materials to be provided to non-English speaking subjects, such as surveys and questionnaires. The investigator should describe how communication with non-English speaking subjects will be facilitated throughout the course of the study.

4.10. Recruitment Process and Documents:

Since recruiting materials (*e.g., advertisements, flyers, phone scripts, newspaper ads, radio and television announcements, bulletin tear-offs, Internet postings, and posters*) are part of the informed consent process and the subject selection process, the IRB must review, approve and stamp all recruiting procedures and material prior to their use by an investigator.

A. **When to Submit Recruiting Materials to the IRB:**

1. Direct advertising for research subjects is considered the start of the informed consent process. As such, recruiting materials must be submitted with the research protocol for initial review.
2. A description should be provided regarding the manner in which the materials will be distributed/utilized and by whom (*i.e. clinic staff will hand flyer to patients or e-mail announcement distributed through COM-R Mass mail)*.
3. Recruiting materials may state that subjects may be compensated or reimbursed, but specific dollar amounts should not be a major feature of the advertisement.

4. For recruiting materials that are to be taped for broadcast, transcripts must be submitted for review and approval. The final taped message may be approved via expedited procedures.
5. The recruiting material must not be unduly influential in its approach and/or should not promise a certainty of cure or other benefits beyond what is outlined in the informed consent document and the research protocol.
6. If investigational agents are involved in the research, no claims may be made (*explicitly or implicitly*) that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device.
7. Recruiting materials may not use the terms "new treatment", "new medication", or "new drug" without explaining that the test article is investigational, i.e., not approved by the FDA. A phrase such as "receive new treatments" leads subjects to believe they will be receiving newly improved products of proven worth.
8. Do not promise "free medical treatment", when the intent is only to say that subjects will not be charged for taking part in the research investigation.

B. **Items that Must Be Included in Recruiting Materials**:

1. Research project title or identifier (*i.e. smoking cessation*).
2. A description of the type of research and purpose of the research.
3. The word "research" must be included in the description. It is not enough to imply that the subject is being recruited for research by just using the word "study".
4. A name of the person or office to contact and the number to call for further information.
5. The COM-R research protocol number and the fact that the research is being performed at COM-R.
6. The Principal Investigator's name, department, and address.
7. The specific location of the research.
8. Footer with version # and date.
9. Space for the COM-R IRB approval stamp (*approximately 2.5 x 1.5 inches*).

C. **Information that Must be Included in Recruiting Materials:**

1. In summary form, the criteria that will be used to determine eligibility for participation in the research.
2. A description of the time commitment and duration of the subject's participation and number of visits required for the research.
3. A brief description of the benefits of the research, if any (*e.g., smoking cessation*).

4.11. Informed Consent / Assent/ Parental Consent Process and Documents

The PI and their research staff must develop an informed consent process and method of documentation appropriate to the research type and the study population, with an emphasis as to the importance of participant comprehension and voluntary participation.

The PI is responsible for obtaining legally effective informed consent from the participant or the participant's legally authorized representative except in cases where in the IRB has granted an alteration or waiver of informed consent. In cases of waiver of documentation of informed consent, the PI must follow the requirements in the applicable COM-R HSPP policies and procedures.

The PI must follow the applicable COM-R HSPP policies and procedures in obtaining informed consent.

References:
21 CFR 50.20, 21 CFR 50.25(a)(7), 21 CFR 50.27(a), 21 CFR 50.27(b)(2)
45 FR 46.116, 45 CFR 46.116(a)(7), 45 CFR 46.117(a)

4.11.1. Requirements for Informed Consent Process:

The COM-R IRB requires investigators to obtain prospective informed consent of each research subject or their legally authorized representatives before they are included in research (*including screening procedures*), except where a waiver of informed consent is granted by the IRB.

Investigators are responsible for incorporating the basic elements of informed consent, FDA requirements, applicable additional elements of informed consent, and COM-R requirements in the informed consent. When a basic or applicable element is absent, the investigator must request a waiver or alteration of informed consent from process to the IRB.

Informed consent is an ongoing process which begins with recruitment and continues throughout the subject's participation in the study. In order to approve research involving human subjects, the COM-R IRB reviews the informed consent process and documents to assure:

A. The required elements as defined by the Federal Regulations, VA handbook 1200.05 and COM-R policy and any additional elements that are deemed appropriate by the IRB are included; and

B. The research is presented in an organized and easily understood fashion that allows the subjects or their representatives to make an informed and voluntary decision concerning participation. Health literacy standards are required at COM-R for all informed consent documents. The reading level should be a 5th to 8th grade level, when possible.

The IRB must approve the informed consent process and method of documentation, indicating whether the proposed consent process is appropriate for the proposed research activities and the target population as a part of the overall IRB approval of the study.

The COM-R IRB may require that information, in addition to that specifically required by applicable regulations, be given to subjects when in its judgment the information would meaningfully add to the protection of the rights and welfare of subjects or improve subject understanding and voluntary decision-making.

4.11.1.1. Informed Consent: IRB Review of the Informed Consent Process:

A. Submission. Investigators submit the proposed informed consent document(s) with their initial and continuing review applications for IRB review and approval. This documentation is also submitted with amendments when the proposed changes alter the informed consent document or process.

B. IRB Documentation. The IRB documents their review and determinations involving the consent process in the meeting minutes or, when review occurs under expedited conditions, review guides.

C. Consent Process. The IRB reviews that protocol and IRB application to ensure that:

1. It identifies who will obtain informed consent and that consent is obtained by research personnel with human subjects' protection training;
2. Modes of communication and materials are appropriate to the targeted by research population, including use of the targeted subject population's primary language and/or reading level;
3. Conditions under which consent is sought provide the potential subject or their representative sufficient opportunity to consider whether or not to participate and minimize possibility of coercion or undue influence;
4. Informed consent does not include any exculpatory language through which the subject or representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, sponsor, institution, or agents from liability for negligence (examples of what does and does not represent exculpatory language can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/exculp.htm).

D. **Basic Elements of Consent.** The IRB verifies that the informed consent document contains the following basic elements of consent stipulated at 45 CFR 46.116(a) and 21 CFR 50.25(a);

1. States that the study involves research;
2. Explains the purposes of the research;
3. States the expected duration of the subject's participation;
4. Describes the procedures to be followed and identifies any which are experimental;
5. Describes reasonably foreseeable risks or discomforts to the subject;
6. Describes any benefits to the subject or to others which may reasonably be expected from the research;
7. Discloses appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
8. Describes the extent, if any, to which confidentiality of records identifying the subject will be maintained;

a. The consent must note the possibility that the FDA may inspect the records for FDA regulated research; and

b. Consent should also note others who may have access, including, as applicable, the sponsor, funding agencies, COM-R RSS, and State of Illinois auditors.

9. When applicable, explains whether any compensation and whether any medical treatments are available if any injury occurs and, if so, what they consist of, or where further information may be obtained.
   a. COM-R template consent forms contain options for language deemed acceptable for injury compensation;

   b. Language other than one of the COM-R acceptable options requires review and approval by University Counsel; and

   c. Injury compensation language in the consent must agree with that in the Clinical Trial Agreement (CTA).

10. Explains who to contact for answers to pertinent questions about the research and research subjects' rights, and who to contact in the event of a research related injury to the subject; and

11. States that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

E. **Additional Elements of Informed Consent.** The IRB determines whether one or more of the following additional elements of informed consent must be provided to subjects:
   1. Statement that the particular treatment or procedure may involve risks to the subject (*or to the embryo or fetus, if the subject is or may become pregnant*) which are currently unforeseeable;

   2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

   3. Any additional costs to the subject that may result from participation in the research;

   4. Consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

   5. Statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject; and/or

   6. Approximate number of subjects involved in the research.

F. **FDA Regulated Research.** For all research involving a test article *(i.e., investigational drug, device or biologic)* regulated by the FDA, informed consent documents must, as applicable:

1. Per COM-R requirements, inform subjects that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies are not appropriate when the purpose of the study includes determination of safety.

2. Inform subjects, for studies that also evaluate the effectiveness of the test article, of that purpose, but should not contain claims of effectiveness;

3. If the research involves an investigational drug, device, biologic, or Humanitarian Use Device (HUD), states the regulatory status of the agent using explanations designed to be understood by the targeted subject population. For example, "the use of drug [insert name] in this study is considered investigational, meaning it has not been approved by the FDA for marketing in the U.S. for the use being tested in this research."

G. **Vulnerable Populations.** If the research involves groups vulnerable to coercion, the investigator must address and the IRB consider the additional consent concerns described in the COM-R policies and procedures for research involving children, decisionally impaired subjects, pregnant women or fetuses, neonates, or prisoners. When the research will involve COM-R students or employees, the consent should include the COM-R informed consent template disclosure statements for these subjects.

H. **COM-R Specific Consent Requirements.**

1. The COM-R informed consent templates provide investigators with standard formatting and language for sections (*e.g., voluntary participation, other alternatives, new information, privacy and confidentiality, compensation for injury, answers to question*) of the consent documents.

2. Any deviation from the standard formatting and informed consent template language requires IRB approval.

3. The consent document should be written in the second person (i.e., "You have been invited to participate . . ." or "Your participation in the research is voluntary") to help convey the message that the subject is choosing to participate. The first person should be used only in the final section of the consent form, indicating the subject's agreement to participate.

4. The consent document for funded research should indicate the name of the sponsor or funding agency and that they are providing funds (or test article or other support) for the conduct of the research;

5. Investigator discloses any conflicts of interest in the consent document following the COI disclosure agreement (SEAM) worked out with the COI

office. The IRB reviews and approves the disclosure language in the consent document.

6. If a Certificate of Confidentiality/Privacy Certificate has been obtained, consent states the terms and limitations provided by the Cerificate (Refer to COM-R HSPP policy and procedure *Approval Criteria; Confidentiality.*)
7. Consent informs subject of their responsibilities during the study.
8. State whether biological materials obtained as part if the research will be used for commercial development and, if so, whether there are plans to compensate or allow the subject to share in the profits from this development.
9. Provide name, department and contact information for investigator.

4.11.1.2. Waiver or Alteration of Consent:

A. The COM-R IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent. The investigator must show, and the IRB must document in a protocol specific manner that:
   1. The research involves no more than minimal risk to the subjects;
   2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
   3. The research could not practicably be carried out without the waiver or alteration;
   4. When appropriate, the subjects will be provided with additional pertinent information after participation; and
   5. The research is not subject to FDA regulation.

B. Department of Defense. If the research subject meets the definition of "experimental subject", a waiver of consent is prohibited unless a waiver is obtained from the Secretary of Defense. If the research subject does not meet the definition of "experimental subject', the IRB may waive consent.

C. The COM-R IRB requires a waiver of consent and HIPAA authorization for reviewing medical records for recruitment. This is not considered to be in conflict with FDA regulations.

D. Deception. The investigator must obtain an alteration of the informed consent process from the IRB when deception is involved in the research. When the IRB reviews research involving deception, the minutes must document that the IRB made the findings in accordance with 45 CFR 46.116(d). The investigator also must complete the corresponding questions in Appendix J to justify to the IRB the alteration of elements of informed consent meeting the criteria in A. above (46.116(d). The IRB typically requires a plan for debriefing subjects.

E. Consent may also be altered or waived for certain research or demonstration projects conducted by or subject to the approval of state or local government officials that are designed to study, evaluate or otherwise examine:
   (i) public benefit of service programs,
   (ii) procedures for obtaining benefits or services under those programs,
   (iii) possible changes in or alternatives to those programs, or
   (iv) possible changes in methods or levels of payment for benefits or services under those programs, providing the research is not subject to FDA regulation.

F. Refer to the COM-R HSPP policy and procedure, Emergency Use of a Test Article, for a description of when informed consent may be waived under emergency use for FDA regulated research, COM-R does not currently allow planned emergency research.

G. Per FDA Guidance, the FDA also allows waiver of informed consent for FDA-regulated in vitro diagnostic device investigations of leftover human specimens, when investigations meet the criteria for exemption from the InvestigationalDevice Exemptions regulation at 21 CFR812.2(c)(3) and as long as subject privacy is protected by using only specimens that are not individually identifiable.

H. If the IRB reviews the research at a convened meeting, the determination of the waiver of informed consent is documented in the meeting minutes. If the IRB reviews the research for expedited review, the expedited review documents the determination on the reviewer checklist.

4.11.1.3. Waiver of Documentation of Informed Consent:

A. IRB may waive the requirement for the investigator to obtain a signed consent form if it finds either:
   1. That the study presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context, or
   2. That the only record linking the subject to the study is the signed informed consent and the principal risk is harm resulting from breach of confidentiality. Subjects will be given the opportunity to say whether they want documentation linking them to the research and their wishes will govern.

B. The investigator provides a copy of the signed and dated informed consent document to the participant or the participant's representative and keeps the original signed informed consent document as part of the research file. In cases where photocopy equipment is available, the investigator may ask the participant to sign and date two consents, one for the participant to keep and one for the research file. Investigators are strongly recommended to note in the source documentation the

consent process, date consent obtained and that consent was obtained prior to initiating any research procedures.

C. Except when a waiver for obtaining written documentation of informed consent is approved by the IRB, the COM-R IRB requires that the consent form be either:

1. A written consent document that embodies the elements of informed consent required by 45 CFR 46.116 and 21 CFR 50.25. This form may be read to the subject or the subject's legally authorized representative. The investigator must give either the subject or the representative adequate opportunity to read it before it is signed; or

2. A short form written consent document stating that the elements of informed consent required by 46.116 and 50.25 have been presented orally to the subject or the subject's legally authorized representative. The IRB shall approve a written summary of what is to be said to the subject or the representative. When this method is used, a witness is required to attest to the adequacy of the consent process and to the subject's voluntary consent. Therefore, the witness must be present during the entire consent interview, not just for signing the documents. The subject or the subject's legally authorized representative must sign and date the short form. The witness must sign both the short form and a copy of the summary, and the person actually obtaining the consent must sign a copy of the summary. The subject or the representative must be given a copy of the summary as well as a copy of the short form. The person obtaining consent may not be the witness to the consent.

D. **Non-English Speaking Subjects.** Documentation of consent for non-English speaking subjects is discussed in the COM-R HSPP tip sheet, Involvement of Non-English Speaking Subjects in Research at the COM-R.

E. Illiterate English-Speaking Subjects. An individual who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document. Illinois state law allows an individual to "make their mark" on the consent document. Illinois state law allows an individual to "make their mark" instead of a signature, when necessary, and when the process is properly witnessed.

F. Subjects Physically Unable to Talk or Write. An individual who can understand and comprehend spoken English, but is physically unable to talk or write, may be entered into a study if they:

1. Retain the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (i.e., are competent), and
2. Are able to indicate approval or disapproval to study entry.
3. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective

subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended.

G. Blind Prospective Subjects/Prospective Subjects with Motor Difficulties.
Subjects with motor difficulties who are able to fully engage in the consent process but are unable to write their name may "make their mark." This would require a witness being present and the requirements above in 1-6 must be met.

4.11.1.4. VA Research: Please also refer to 4.9.6.6. General Requirements for Informed Consent (Cited from VHA Handbook 1200.05, Appendix C).

A. **VA Consent Document**: For studies in which subjects will be recruited from a VAMC or research will be conducted at VAMC, use of the 10-1086 VA specific consent document is required. (*Jesse Brown VAMC protocols MUST be reviewed by OPRS at UIC*).
   1. The signature and date of a witness, not otherwise involved with the study, as well as the dated signature of the individual obtaining the consent, is required on the VA 10-1086 informed consent document.
   2. In the event that the sponsor or IRB require a witness to both the consenting process and to the subject's signature and the same person serves both roles, this will be documented below the witness's signature line.

B. For JBVAMC research, if someone other than the investigator will conduct the interview and obtain informed consent, the investigator must formally delegate this responsibility and the person so delegated must receive appropriate training to perform this activity.

C. The person obtaining consent should document the consent process in the subject's medical record or the subject's research record. This should include at a minimum, but is not limited to:
   1. The name of the study.
   2. The person obtaining the subject's consent.
   3. A statement that the subject or the subject's legally authorized representative was capable of understanding the consent process.
      a. A statement that the study was explained to the subject.
      b. A statement that the subject was given the opportunity to ask questions.
   4. The PI should place an entry in the progress note when:
      a. The subject was entered into the study.
      b. The subject's involvement in the study was terminated.
   5. Once the consent document is approved by the IRB, each page of the

10-1086 is stamped indicating the date of the most recent IRB approval of the document. The approved, stamped informed consent document becomes a permanent part of the IRB record.

6. If the IRB determines that the protocol should be "flagged" in the medical record, investigators are responsible for ensuring the signed consent forms are scanned into the electronic medical record (CPRS).

4.11.1.5. Informed Consent Process: Investigator Responsibilities:

A. Informed consent is a continuous process. It starts with the initial presentation of a research activity to a prospective subject and continues until the subject ends their participation or the study closes. The investigator must assure that an ongoing exchange of information between the research team and subjects (including persons giving consent or permission for others) are maintained throughout the course of the study.

B. The investigator describes the informed consent process in the protocol and IRB application.

C. The COM-R IRB requires that the investigator or other study personnel who conduct the consent process present the information accurately and in a manner minimizing the possibility of coercion or undue influence.

D. The consent process must allow prospective subjects sufficient time to consider whether to participate in the study, consult with others and have all their questions answered.

E. The IRB may require investigators to develop a formal plan to assess and confirm that the subject understands the consent. This may include the use of a written tool, requiring a friend or family member to be present, requiring a waiting period or observation of the consent process by a representative of the IRB.

F. Delegation of Responsibility for Obtaining Consent: If the Principal Investigator is delegating the responsibility for conducting the consent interview and obtaining informed consent to someone else on the research team, the PI must formally delegate this responsibility to this person or persons by naming them in the research application and in the research records (*delegation log*). The person must have received COM-R IRB training and be up to date on COM-R IRB continuing education requirements to perform this function.

G. Providing Subjects with Notice of Additional Reporting Requirements. Investigators and the IRB should be aware of when the informed consent document must include a statement explaining that confidentiality might be breached due to Illinois reporting laws, including for positive HIV status, elder and child abuse, cancer, and certain infectious diseases.

H. Any changes in the informed consent documents or processes after IRB approval must be submitted as a modification to the IRB for review and approval prior to implementation.

References:
21 CFR Part 50
38 CFR 16.116
45 CFR 46.109(b), 45 CFR 46.111(b), 45 CFR 46.116, 45 CFR 46.117, 45 CFR 46.408(c)
OHRP Informed Consent FAQs
OHRP Informed Consent Checklist
OHRP Informed Consent Tips
OHRP Exculpatory Language in Informed Consent November 15, 1996
VHA Handbook 1200.05, Appendix C
JBVAMC Consent Template
UIC Social and Behavioral Sciences Informed Consent Template
UIC Biomedical Sciences Informed Consent Template

4.12. Research in the COM-R Clinics:

HIPAA regulation provides strict guidelines on accessing and using patient information. However, there are provisions that allow researchers to access and use patient information for research purposes. Compliance with the following guidelines is mandatory. All employees of the University of Illinois Rockford must abide by the University policies related to privacy and security of patient health information and may not access, extract, or provide PHI to any person without providing the required IRB approval letter to the clinic manager who then notifies COM-R Director of Compliance/Privacy Officer. All researchers must be aware that PHI cannot be stored on their laptops and or flash drives. If PHI is being stored, the researcher must contact the Director of Compliance/Privacy Officer to make arrangements for either laptop encryption or be provided with an encrypted flash drive.

Federal law allows four methods for a researcher to use personal health information in research.

1. **Preparatory to Research:** Accessing patient medical or billing records to develop a research protocol - Submit "Appendix H" and the "Determination of Whether an Activity Represents Human Subject Research" form to the IRB to receive a letter that provides verification of your administrative review. This letter must be given to the Director of Compliance/Privacy Officer who will forward to the clinic manager. The letter must be provided before the data is accessed by the researcher.

2. **De-identified Data Set:** Accessing medical or billing records to extract de-identified information - Submit "Appendix H" with a "Claim of Exemption" and/or other applicable forms to the IRB to receive an "Exemption Granted" status letter. This letter must be provided to the Director of Compliance/Privacy Officer who will forward to the clinic manager. The researcher should expect that it may take some time for the clinic manager to produce de-identified information.

3. **Limited Data Set:** Accessing medical or billing records to extract a subset of information (PHI) that only contains the following identifiers linked to the subject:
   - city, state, zip code,
   - elements of date such as date of birth, death or service

The other specific identifiers included in the following list may **NOT** be included in the health information that is being received by the research team. **The use of a Limited Data Set requires a Data Use Agreement to be in place.** Submit "Appendix H", a "Data Use Agreement" (*available on the RSS webpage*) with the appropriate application to the IRB to receive a letter that grants a HIPAA waiver. (***NOTE:*** *Make sure to request a waiver of Informed Consent on the application when a HIPAA waiver is being requested*). This letter must be provided to the Director of Compliance/Privacy Officer who will forward to the clinic manager.

The HIPAA Privacy Rule regulations [*45 CFR 164.514(b)*] lists 18 specific identifiers that must be removed from the health information before the researcher obtains the information for it to be considered not identifiable.

The list includes:

- Name/initials
- Street address, city, county, precinct, zip code and equivalent geocodes
- All elements of dates (*except year*) directly related to an individual (*date of birth, admission date, discharge date, date of death*);
- Elements of date, including year, for persons 90 or older
- Telephone number
- Fax number
- Electronic mail address
- Social Security Number
- Medical record numbers
- Health plan identification numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web addresses (URLs); Internet IP addresses
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images
- Any other unique identifying number, characteristic or code

4. **Authorization provided by patient:** Authorization forms used for clinical purposes **DO NOT** meet the same legal standard that is required in research. Please contact Research Support Services at 815-395-5942 for more information on obtaining Authorization Templates, which are available on IRBNet and on the RSS Web page.

TRACKING OF RESEARCH PARTICIPANTS:

All PHI gained through a Waiver of HIPAA Authorization must be disclosed if a patient provides a written request for information. Individuals are entitled to a single accounting every 12 months without charge. Additional requests within a 12-month period may be subject to a "reasonable, cost-based charge" provided that this is detailed in the Notice of Privacy Practices.

Federal law requires an institution to provide:

1. List of all protocols where their PHI may have been disclosed pursuant to a waiver.
2. Researcher's name and contact information.

3. Where there are 50 or fewer records the accounting must meet:
   a) Date of the disclosure (*if multiple the start and stop dates and frequency*),
   b) The name of entity or person who received the PHI and, if known, the address of each entity or person,
   c) A brief description of the PHI disclosed, and
   d) A brief statement of the purpose of the disclosure that reasonably informs the individual of the basis for the disclosure.

NOTE: *Covered entities have 60 days to meet this request. An additional 30 day extension is allowed if the requestor is provided with a written explanation for the delay by the institution that is being asked to provide the information. Any letter received from a patient should be forwarded to the Director of Compliance/Privacy Officer who will then forward the information to the clinic manager.*

These letters are considered high priorities that have severe consequences in not responded to immediately.

IMORTANT: Records **MUST** be kept that detail all PHI that has been accessed for the last six years.

4.12.1. Research in the COM-R affiliated clinics (*RMED*)

All students conducting research in the RMED affiliated clinics that wish to use PHI must contact the privacy officer for that clinic and provide a letter of support to COM-R IRB along with the Application and Appendix H. The clinic may require an external data use agreement before releasing the PHI after attaining COM-R IRB approval for the protocol. Please check with the RMED student advisor to see whether the RMED clinic has an IRB that also requires review and notification that the COM-R IRB will be reviewing the student study as the IRB of record.

Definitions:

Use: The sharing, employment, application, utilization, examination or analysis of information written the entity that maintains the information.

Disclosure: Release, transfer, provision of access to, or divulging in any manner of information by the entity holding the information. Research authorization must be in writing – must be signed, must contain/include:

Research: Defined by DHHS Common Rule (*45 CFR 46.102*) as data collected in a systematic method that is used to contribute to generalizable knowledge.

QA/QI: Loosely defined as by the intent of a project to improve the services that can directly or indirectly benefit the patient or employee. These types of studies are for internal use only and not meant for publication.

4.13. FDA Regulated Research:

Research Involving the Use of Drugs, Biologics or Medical Devices:

The COM-R HSPP follows federal, state and institutional regulations in reviewing research involving the use of drugs, biologics or devices.

When reviewing research involving the use of a drug or biologic, the COM-R IRB determines whether the drug requires an IND or the investigation meets one of the FDA exemptions from the requirements to have an IND. If an IND is required, the IRB verifies the IND number prior to approving the research.

When reviewing research evaluating the safety or effectiveness of a device, the IRB determines whether the device requires an IDE, fulfills the requirements for an abbreviated IDE, or the protocol meets one of the FDA exemptions from the requirement to have an IDE. If an IDE is required, the IRB verifies the IDE number prior to approving the research.

The COM-R IRB does not have oversight responsibility for use of a marketed drug, biologic or device in the course of medical practice for a non-approved ("*off label*") indication. COM-R policy currently does not allow planned emergency research.

4.13.1. Procedure: Research Involving Drugs and Biologic Products:

A. Investigators must submit to RSS for IRB review the documents described in the Initial Review Application: Health and Biological Sciences, including Appendices A-1 and E.

B. Initial review for IRB approval of a study involving the research-related administration of a drug or biologic occurs at a convened IRB meeting, unless the research activities present no more than minimal risk and an IND is not required in accordance with expedited review categories.

C. An IND is commonly required for any clinical study that proposes the use (*e.g., as a research tool to explore a biological phenomena or disease process*) or evaluation (*i.e., pharmacokinetics, safety and/or effectiveness*) of an unapproved drug or biological product or unapproved indication or use for a marketed drug or biologic.

D. If the investigator is requesting the drug or biologic (*unapproved or marketed*) be exempt from IND requirements, the investigator must justify this request on Appendix A-1. Alternatively, the investigator may provide the IRB with communications from the FDA indicating that an exemption from the IND regulations has been granted.

E. The FDA has issued a specific guidance for the use of lawfully marketed drugs and biologicals in oncology protocols. This guidance provides details and examples of those regiments that do and do not require an IND. (*Refer to FDA Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer*).

F. If the investigator has not provided an IND or letter from the FDA granting an exemption from IND requirements, the IRB reviews and determines whether the research meets one of the FDA exemption requirements below. The IRB documents their determination in the meeting minutes or, when the review occurs by expedited procedures, the expedited reviewer's Review Guide.

1. **Exemption 1:**
    a. The drug product is lawfully marketed in the United States.

b. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.

c. If the drug that is undergoing investigation was lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.

d. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (*or decreases the acceptability of the risks*) associated with the use of the drug product.

e. The investigation is conducted in compliance with 21 CFR 50 and 56.

f. The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (*Promotion and charging for investigational drugs*)

2. A clinical investigation involving use of a placebo does not require an IND if the investigation does not otherwise require submission of an IND.

3. **Exemption 2:**
   a. A clinical investigation involving an in vitro diagnostic biological product hat meets the following:
      (1) Product is blood grouping serum, reagent red blood cells, or anti-human globulin;
      (2) The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
      (3) The diagnostic test was shipped in compliance in 21 CFR 312.160.

4. **Exemption 3:** A drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

5. **Exemption 4:** Clinical bioavailability or bioequivalence study are exempt from the requirement for an IND except when one or more of the criteria described below are met:
   a. The drug product contains a new chemical entity (21 CFR 320.31 (a)(1)), radioactively labeled drug product (21 CFR 320.319a)(2)) or cytoxic product (21 CFR 320.31(a)(3)).

   b. The study involves a drug product containing an already approved, non-new chemical entity and is:
      (1) A single-dose study in normal subjects or patients where either the maximum single or total daily dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application or abbreviated new drug application,

(2) A multiple-dose study in normal subjects or patients where either the single or total daily dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application or abbreviated new drug application, or

(3) A multiple-dose study on an extended release product on which no single dose study has been completed.

6. **Exemption 5:** A clinical bioavailability or bioequivalence study being conducted for approval of an abbreviated new drug application or supplemental new drug application other than studies described in 5.a. and 5.b. above as long as samples of the reference standard and test article are retained as described in 21 CFR 320.38 and 320.63.

G. Clinical investigations that are exempt from IND requirements still require IRB review and approval.

H. If the IRB determines that there may potentially be significant risk or decreased acceptability involved with the use of a drug utilizing a different route of administration, dose, or in a non-FDA approved population and/or disease, the IRB can request that the investigator contact the FDA for review of the proposed clinical investigation to determine whether the use qualifies for an exemption from the IDN requirements.

I. The research application involving the use of a drug or biological product, unless the research is exempt from the IND regulations, must include evidence that the FDA has issued an Investigational New Drug (IND) number. The IRB Assistant Directors or IRB Coordinators will confirm that the IND number provided in the IRB submission matches that recorded on the sponsor protocol, communication from the sponsor, or communication from the FDA. The Investigator's Brochure is not an acceptable mechanism for verification. Validation of the IND number is required before IRB approval.

J. Handling of Investigational Drugs or Biologics. Not to use the IDS for storage, control and dispensing of the drug or biologic exists. If the investigator opts to handle the investigational agent themselves, a process for handling the investigational drug must be provided to the IRB on Appendix A-1 for review and approval. The IRB obtains the input of IDS or other qualified pharmacist in confirming the adequacy of the drug control plans. Drug accountability records along with storage and dispensing of investigational drugs are subject to audit to IDS and the OVCR Research Compliance Office.

4.13. 2. Research Involving Medical Devices:

A. Investigators must submit to RSS for IRB review the documents described in the Initial Review Application: Health and Biological Sciences, including Appendix A-2.

B. Initial review for IRB approval of a study involving the research-related use of a medical device may be reviewed by expedited procedures when research activities are:

No greater than minimal risk, and

(i) an IDE is not required; or

(ii) the device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling. Clinical investigations for which an IDE is required are reviewed at a convened meeting.

C. **Research with devices falls into three categories:**

1. Investigations exempted from the IDE regulations;
2. Investigations of significant risk devices to determine safety and effectiveness of the device;
3. Investigations of nonsignificant risk devices to determine safety and effectiveness of the device.

D. When the investigator indicates on Appendix A-2 that the research is exempt from the requirement for an IDE and has not provided a letter from the FDA granting an exemption, the IRB reviews and determines whether the research meets one of the FDA exemption requirements. The IRB documents their determination in the meeting minutes, or, when the review occurs by expedited procedures, the expedited reviewer's Review Guide.

1. A device legally marketed in the U.S. that is used or investigated in accordance with the indications in the FDA-approved labeling.
2. A diagnostic device (*that is, an in vitro diagnostic device*) if the testing:
    a. Is noninvasive.
    b. Does not require an invasive sampling procedure that presents significant risk,
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
3. A device undergoing consumer preference testing, a testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
4. A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distri bution.
5. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
6. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the

indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

E. Clinical investigations that are exempt from IDE regulations still require IRB review and approval.

F. **Significant Risk (SR) versus Non-Significant (NSR) Risk Devices**.

1. Unless exempt from the requirements for an IDE, an investigational device must be categorized as either a SR device or a NSR device.

2. The initial risk assessment is made by the sponsor.

3. Next, the IRB must review the sponsor's SR or NSR assessment and modify the determination if the IRB disagrees with the sponsor. If the FDA has already made the SR or NSR determination, their determination is final and the IRB does not need to duplicate effort.

4. The IRB's determination regarding the appropriate SR/NSR category must occur at a convened meeting. The determination and reason for the determination are documented in the meeting minutes. The documentation should include the SR/NSR determination letter from the FDA, if the FDA has already made a determination.

5. The sponsor through the investigator provides the IRB with the following information: explanation of their risk determination, description of device, reports of prior investigations, proposed investigational plan, subject selection criteria and other information pertinent to the IRB deliberation.

6. The IRB's risk determination should consider the device, the proposed use of the device and any protocol-related procedures (*e.g., surgery*). The following criteria for a SR device guide the IRB in making their determination:
   a. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
   b. Is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject.
   c. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
   d. Otherwise presents a potential for serious risk to a subject.

7. If the IRB determines that a study, submitted by the sponsor for approval as a NSR device represents a SR device, the IRB Assistant Director or coordinator notifies the investigator and sponsor of this decision. The investigator will be instructed to re-submit the protocol as a SR device study and to provide

documentation from the sponsor of an approved IDE (*i.e., copy of the letter from the FDA providing approval or conditional approval of the IDE*).

8. If the IRB concurs with the sponsor's assessment of a NSR device, the IRB proceeds with its review and approval of the device study following the criteria at 21 CFR 56.111. The study may begin without submission of an IDE application to the FDA. Conduct of the NSR device study must follow the "abbreviated" requirements described at 21 CFR Sec. 812.2(b).

G. **SR Device Research**.

1. When research is submitted for IRB review and approval as a SR device, the investigator is responsible for providing the IRB with the IDE number and a copy of the letter from the FDA-providing approval or conditional approval of the IDE to confirm the validity of the IDE. The IRB Assistant Directors or coordinators will confirm submission of this documentation prior to IRB approval.

2. Initial IRB review occurs at a convened meeting.

3. For SR devices that are implanted, the IRB must assess the exit strategy for the device to ensure that human subjects are adequately protected once the study ends, if applicable.

H. **Handling of Investigational Devices.**

When the COM-R IRB serves as the IRB record for clinical investigations of devices at other institutions, the investigator must describe the process for handling the investigational device. The IRB will seek input from a qualified individual from that institution to confirm their concurrence with the plan before approving the research.

4.13.3. 510 (k) Premarket Notification (PMN):

A. Any investigator considering the submission of a 510(k)/PMN may contact the COM-R RSS for guidance.

B. The FDA must be notified 90 days in advance of intent to market a medical device.

C. Submission of a PMN to the FDA is required if there is the intention to introduce a device into commercial distribution for the first time or to reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected.

D. The change or amendment could relate to the design, material, chemical composition, energy source, manufacturing process, or intended us.

4.13.4. Radioactive Materials:

Oversight of radioactive materials used in research at UIC is handled by the Radioactive Drug Research Committee, a subcommittee of the UIC Human Radiation Safety Committee in the UIC Environmental Health and Safety Office, which is chartered as a Radioactive Drug Research Committee (RDRC) by the FDA under 21 CFR 361.1. Most research involving

human subjects and radiation is covered by an IND or an IDE, and must be reviewed and approved by the IRB. IRB review occurs after review and approval is obtained from the RDRC. The radiation safety section of the Environmental Health and Safety Office provides assistance to investigators in planning human research studies and obtaining the necessary approvals for human research studies involving radioactive materials (http://www.uic.edu/depts./envh/).

4.13.5. Expanded Access to Investigational Drugs and Devices:

A. **Investigational Drugs**.

1. Treatment IND.

a. Treatment IND [21 CFR 312.34 and 312.35] provides a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks.

b. Four requirements must be met before a treatment IND can be issued:

1) The drug is intended to treat a serious or immediately life-threatening disease;

2) There is no satisfactory alternative treatment available;

3) The drug is already under investigation, or trials have been completed; and

4) The trial sponsor is actively pursuing marketing approval, a treatment use under a treatment IND may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

c. COM-R policy is that treatment IND studies require prospective IRB review and informed consent.

2. Group C Treatment IND.

The "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. they can generally be administered by properly trained physicians without the need for specialized support care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent

document which must be used if there has been no local IRB review. COM-R policy is that Group C treatment IND studies require prospective IRB review and informed consent.

3. Parallel Track. The FDA's Parallel Track policy [57 FR 13250] permits winder access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

4. Emergency Use. Refer to the UIC HSPP policy Emergency Use of Test Article.

B. **Investigational Devices**.

1. Compassionate Use. The FDA allows the use of an unapproved device in circumstances where the device is the only option available for a patient faced with a serious or life-threatening condition that does not meet the criteria of an emergency. Prior FDA approval is required before compassionate use occurs. As a first step, the clinician should seek the approval of the IDE holder and provide them with the following information:
   a. Description of the patient's condition and circumstances necessitating,
   b. Discussion of why alternative therapies are unsatisfactory,
   c. An identification of any deviations from the approved labeling required to treat the patient and
   d. Patient protection measures that will be followed (*refer to Emergency Use of Test Article" policy*). The IDE holder must then submit an IDE supplement to the FDA for approval.
   Once FDA approval is obtained, the investigator should submit the protocol including appropriate schedule for monitoring the patient, COM-R Emergency Use application form, information provided to the FDA concerning the 4 points above, informed consent document and copy of the letter from the FDA approving the IDE supplement to the IRB for review and approval. Subject should not be treated with the device until FDA and IRB approval are obtained. Following compassionate use of the device, a follow-up report should be submitted to FDA in which summary information regarding patient outcome is presented. If problems occurred as a result of device use, they should be discussed in the follow-up report. A copy of the follow-up report should be submitted to the COM-R IRB.

2. Treatment Use.
   a. Approved IDEs specify the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in study. During the course of a clinical trial, if the data suggest that the device is effective, then the trial may be expanded to include additional patients with life-

threatening or serious diseases. To qualify for a treatment use IDE, the disease or condition must be life threatening or serious, and patients must have no comparable or satisfactory alternatives to the investigational device. FDA will consider the use of an investigational device under a treatment IDE if all of the following criteria are met:

(1) The device is intended to treat or diagnose a serious or immediately life threatening disease or condition;

(2) There is no comparable or satisfactory alternative device or other therapy to treat or diagnose that stage of the disease or condition in the intended patient population;

(3) The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or the clinical trials have been completed; and

(4) The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

b. Specific requirements for a treatment IDE application are available. at http://www.fda.gov/cdrh/devadvice/ide/early.shtml#treatmentuse.

c. Treatment use may begin 30 days after FDA receives the treatment IDE submission, unless FDA notifies the sponsor otherwise.

d. A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is considered an "investigator" under FDA regulations and is responsible for meeting all applicable investigator responsibilities, including responsibilities to obtain prospective IRB approval and informed consent.

3. Continued Access to Investigational Devices.

a. The sponsor of a clinical investigation is permitted to continue to enroll subjects while a marketing application is being prepared by the sponsor and/or reviewed by the Agency if there is:

1) A public health need for the device and

2) Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.

b. The continued enrollment of subjects in an investigation while a marketing application is being prepared by the sponsor and/or reviewed by ODE is known as an "extended investigation." A sponsor's request for an extended investigation is as an IDE supplement. There is significant overlap between the treatment IDE regulation and the Continued Access Policy. The continued

access policy and the treatment IDE regulation are intended to provide additional access to an unapproved device, once preliminary evidence regarding safety and effectiveness is available to FDA. However, because a treatment IDE can be submitted earlier in the IDE process, i.e., once promising evidence of safety and effectiveness has been collected under the IDE but while the clinical study is ongoing, it provides access to a wider group of patients at an earlier stage in the IDE process. The treatment IDE regulation also has a more narrow application than the Continued Access Policy in that treatment use is intended to address only those patients who have an immediately life-threatening or serious disease or condition whereas the Continued Access Policy, which is applied after completion of the clinical trial, may be considered for any clinical investigation.

4. Emergency Use. Refer to the COM-R HSPP policy Emergency Use of Test Article. 4.13.7.

5. Humanitarian Use Device. Refer to the COM-R HSPP policy Humanitarian Use Device (HUD). 4.13.8.

References:

21 CFR 312.21 CFR 320.21 CFR 312.160.21 CFR 312.7, 21 CFR 812.21 CFR 803.30
FDA Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or
Biological Products for the Treatment of Cancer
FDA Guidance: Significant Risk and Nonsignificant Risk Medical Device Studies
Draft Guidance for Industry and FDA Staff – In Vitro Diagnostic (IVD) Device Studies Frequently Asked Questions –
FDA Guidance on IDE Policies and Procedures, January 20, 1998.

4.13.6. Definitions:

BIOLOGIC: A biological or related product derived from living sources (*e.g., humans, animals, microorganisms*) and regulated by the FDA, including blood, vaccines, allergenics, tissues and cellular and gene therapies. Studies of unlicensed biologics are generally regulated according to the IND regulations. FDA regulations related to the general use and licensing of biologics are found in 21 CFR 600 and 601.

CLINICAL INVESTIGATION: Any experiment in which a drug (*or biologic or device*) is administered or dispensed to, or used involving, one or more human subjects. In this context, experiment refers to any use of a drug except for the use of a marketed drug in the course of medical practice. (21 CFR 312.3(b)).

DEVICE Is an instrument, apparatus, machine or similar article that is used for the diagnosis, mitigation, cure, prevention or treatment of disease and does not work through chemical action or metabolism within the body.

DRUG: A product that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or intended to affect the structure or function of the body and achieves its intended effect through chemical action or metabolism within or on the body.

FOOD AND DIETARY SUPPLEMENTS: These are generally are not regulated as drugs. However, those that are intended or promoted to be used in the diagnosis, cure, mitigation, treatment or prevention of disease are considered drugs.

INVESTIGATIONAL DEVICE: Medical device that is the subject of a clinical study designed to evaluate the effectiveness or safety of the device, or a clinical evaluation of certain modifications or new intended uses of a legally marketed device. Clinical investigations that involve FDA regulated devices are subject to the requirements of 21 CFR 812.

INVESTIGATIONAL DEVICE EXEMPTION APPLICATION (IDE): An IDE exempts an unapproved or uncleared device (*or an approved or cleared device for an unapproved or uncleared indication*) in a research study involving humans (*i.e., an IDE is an investigational exemption*) from certain statutes and regulations. With this exemption, the unapproved or uncleared device can be shipped and used in human research.

INVESTIGATIONAL NEW DRUG: Refers to an unapproved drug or biologic (*or approved drug or biologic for an unapproved indication*) used in an FDA-regulated clinical investigation. The term also includes biological products used in vitro for diagnostic purposes. Clinical investigations that involve FDA regulated drugs are subject to the requirements of 21 CFR 312.

INVESTIGATIONAL NEW DRUG APPLICATION (IND): An IND exempts an investigational new drug from pre-marketing approval requirements that would otherwise be applicable and allows the drug to be lawfully shipped for the purpose of conducting clinical investigations of that drug (21 CFR 312.1(a)).

NONSIGNIFICANT RISK DEVICE: A device not meeting the definition of SR device. Examples of significant and nonsignificant risk devices are available at http://www.fda.gov/MedicalDevices/DeviceReglationandGuidance/GuidanceDocuments/ucm126622.htm.

PREMARKET APPROVAL (PMA) APPLICATION: A PMA is the most stringent type of marketing application for medical devices. FDA approves a PMA based on presence of sufficient valid scientific evidence and reasonable assurance that the device is safe and effective for its intended use. Once approved, it can be marketed and sold within its approved labeling.

PREMARKET NOTIFICATION (510(K)): A 501(k) application is submitted to FDA before a manufacturer plan to market a device. If the FDA agrees that the new device is substantially equivalent to a legally marketed device for which a PMA is not required, he manufacturer may market it immediately. FDA does not require clinical data for most 510(k)s. However, it clinical data are necessary to demonstrate equivalence, the clinical study must comply with IDE, IRB and human subject protection regulations.

SIGNIFICANT RISK DEVICE: Significant risk device (SRI) is an investigational device that:

(1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
(2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject;
(3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
(4) otherwise presents a potential for serious risk to a subject. The SR determination encompasses the proposed use and not the device alone (*e.g., need for additional procedures, such as surgical implantation, as part of the study should be included in risk assessment*).

4.13.7. Emergency Use of Test Article:

The stipulation for emergency use of a test article (*i.e., investigational drugs, agents, biologics, or medical devices*) in the FDA regulations represents an exemption from prospective IRB review and approval for the use in a single patient of an investigational drug, biologic or medical device that does not have premarket approval or other approval. Any subsequent use of the test article at the institution requires prospective convened IRB review and approval, unless emergency treatment to a second individual arises before the IRB has had sufficient time to convene a meeting to review the issue. (*Refer to FDA Information Sheets: Emergency Use of an Investigational Drug or Biologic, 1998 Update*). The IRB Chair (*or designee*) determines whether or not this condition has been met.

The COM-R IRB manages the emergency use of investigational drugs, biologics and medical devices in accordance with FDA regulations and COM-R policies and procedures. The FDA and COM-R policies exempt the requirement for review by the convened IRB in emergency use situations.

COM-R policy requires the investigator to notify the IRB and receive acknowledgement of the emergency use from the IRB Chair (*or designee*) before administering the test article. The RSS Specialist may substitute when the IRB Chair or designee is not available. The IRB Chair (*or designee*) reviews the application for emergency use and acknowledges whether or not they concur that administering the test article in this situation meets the emergency use requirements at 21 CFR 56.102(d)). The acknowledgement by the IRB does not represent approval as FDA regulations do not allow expedited approval of research in emergency situations. It should be noted that manufacturers' policies typically require an acknowledge or approval letter from the IRB before the test article will be shipped.

4.13.7.1. Criteria for Emergency Use:

A. The emergency use exemption for an investigational drug, biologic or medical device requires that each of the following criteria in 21 CFR 56.102(d) is satisfied:

1. A life-threatening situation exists requiring treatment with the test article;
2. No standard acceptable treatment is available;
3. Insufficient time is available to obtain IRB approval at a convened meeting; and
4. The activity is not a systematic investigation designed to develop or contribute to generalizable knowledge.

B. The term "life-threatening" encompasses conditions that are both:
1. Life-threatening: diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subject must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
2. Severely debilitating: diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness; loss of arm, leg, hand or foot; loss of hearing; paralysis or stroke.

4.13.7.2. Representation of the Activity as Research:

A. Under FDA regulations, emergency use of a test article meets the FDA definition of a clinical investigation, and the patient receiving the test article meets the FDA definition of a human subject. Therefore, this activity qualifies as human subjects' research under FDA regulations and the FDA may require data from emergency use of a test article to be reported in a marketing application.

B. This activity does not, however, meet the DHHS criteria for human subjects' research, as DHHS regulations at 45 CFR 46 do not allow research involving human subjects to be initiated without prior IRB review and approval. Therefore, COM-R policy is that data from emergency use of a test article may not be reported as part of a prospective systematic investigation designed to develop or contribute to generalizable knowledge. Similarly, this FDA exemption from IRB review is not recognized as VA-regulated human subjects' research.

C. The above policy does not prevent the retrospective use of the data, provided appropriate IRB review and approval of this use has occurred, or the publication of a single patient case history.

4.13.7.3. Requirement for Five-Day Follow-Up Report:

The emergency use of a test article must be reported to the IRB within five working days. (21 CFR 56.104(c)). The report is presented to the IRB at the next convened meeting. The IRB reviews the initial notification, five-day follow-up report, and other relevant information provided by the PI. The IRB Chair (*or designee*)

serves as the primary reviewer on this meeting agenda item. The IRB acknowledges whether or not the emergency use of the test article meets the requirements of 21 CFR 56.102(d) and whether there are any further issues related to the treatment of the subject. The IRB's determination is documented in the meeting minutes and communicated in writing to the investigator. When the emergency use involves the JBVAMC, the R&D Office also receives a copy of the IRB's determination letter to disseminate to the R&D Committee and ACOS for R&D.

4.13.7.4. Requirement for an IND for an Investigational Drug or Biologic:
The emergency use of an investigational drug or biologic that does not have premarket approval or other approval requires an IND. The investigator must contact the manufacturer and determine if the drug or biologic can be made available for emergency use under the company's IND. When an IND does not exist and the situation does not allow time for submission of an IND, the FDA may authorize the shipment of the test article in advance of the IND submission. The request for such authorization may be made by telephone or other rapid communication means. (*21 CFR 312.3*). Contact information for obtaining an emergency IND is available at: http://www.fda.gov/oc/ohrt/irbs/drugsbiologicsNEW.html: http://www.fda.gov/oc/ohrt/irbs/drugsbiologicsNEW.html.

4.13.7.5. Requirement for an IDE for an Investigational (*Unapproved)* Medical Device:
An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an IDE. However, the FDA recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, the FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to the FDA that an emergency actually existed.

A. The requirements for emergency use of an unapproved device are similar to those for an investigational drug:
   1. The patient is in a life-threatening condition that requires immediate treatment;
   2. No generally acceptable alternative for treating the patient is available; and
   3. Because of the immediate need to use the device, there is not time to use existing procedures to get FDA approval for the use.

B. The FDA expects the physician/investigator to follow as may human subjects protection procedures as possible, including:
   1. Obtaining an independent assessment by an uninvolved physician;

2. Obtaining informed consent from the patient or a legal representative in accordance with, and to the extent required by, 21 CFR 50;

3. Documenting informed consent in writing in accordance with, and to the extent required by, 21 CFR 50.27;

4. Notifying institutional officials as specified by institutional policies;

5. Notifying the IRB; and

6. Obtaining authorization from the IDE holder, if an approved IDE for the device exists.

7. COM-R policy requires physician/investigators at a minimum to fulfill procedures 2, 4, and 5.

C. After an unapproved device is used in an emergency use situation, the investigator should:

1. Report to the IRB within five business days and otherwise comply with provisions of the IRB regulations (21 CFR 56);

2. Evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for subsequent use of the device; and

3. If an IDE for the use does not exist, notify the FDA of the emergency use, or if an IDE does not exist, notify the FDA of the emergency use (*CDRH Program Operation Staff 301-594-1190*) and provide the FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results. While prior approval for shipment or emergency use of the investigational device is not required, the use must be reported to the FDA by the IDE sponsor within five working days from the time the sponsor learns of the use. *((21 CFR 812.35(a)(2) and 812.150(a)(4)).*

4.13.7.6. Informed Consent in an Emergency:

A. Even for emergency use of a test article, the physician/investigator is required to obtain and document informed consent from the subject or the subject's legally authorized representative in accordance with FDA regulations (21 CFR 50 subpart B) and Illinois state law. Therefore, a physician/investigator must prepare and submit a consent document with the request to the IRB chair (*or designee*) for emergency use of the test article. The COM-R RSS *Emergency Use* consent template form should be utilized.

B. An exception to the requirement for informed consent is allowed if the physician/investigator and a physician who is not otherwise participating in the clinical investigation certify in writing that all of the criteria at 21 CFR 50.23(a) are met before (*and/or after*) the use of the test article:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article;
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject;
3. Time is not sufficient to obtain consent from the subject's legal representative; and
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

C. If, in the physician/investigator's opinion, immediate use of the test article is required to preserve the subject's life, and time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the physician/investigator should make the determination as to the above four items and, within five business days after the use of the test article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation (*21 CFR 50.23(b)).*

D. In the five day follow-up report notifying the IRB of the emergency use of a test article, the physician/investigator must also inform and provide documentation to the IRB of any exceptions to the requirement for consent (21 CFR 50.23(c)) if this was not done at the time of notification of emergency use. The IRB will subsequently review and determine if the criteria for an exemption from IRB review and the exception for the requirement from consent has been met.

4.13.7.7. Consequence of Failure to Comply:

If notification is not obtained prior to emergency administration of the test article or the five-day follow-up report is not submitted, the IRB may determine that the use of the test article did not meet the criteria for exemption from prospective IRB approval and represents serious and reportable noncompliance to the FDA. The IRB may also decide that the use represents reportable noncompliance to the FDA. The IRB may also decide that the use represents reportable noncompliance when, after reviewing the report, it concludes that the requirements of 21 CFR 56.102(d) for emergency use or 21 CFR 50.23(a) for exception of informed consent are not met.

4.13.7.8. Process and Procedure for Approval of Use of Test Article:

This procedure describes the submission, IRB review, and RSS processing of requests for emergency use of a test article (*i.e., investigational drug, biologic or device*).

A physician/investigator seeking acknowledgement for emergency use of a test article telephones the RSS Office ((815)-395-5942) to alert the COM-R IRB that an Emergency Use Determination application is forthcoming. During non-office hours

or if no one is available at the RSS, the clinician should use either the contact RSS Specialist's e-mail address emergency or emergency contact number.

4.13.7.9. Clearance for Use Procedure:

A. Investigator must identify at what collaborating facility he/she is using the test article.

B. Investigator must specify whether he/she has contacted that facilities IRB office for clearance to see whether the test article has previously been used at that facility and is eligible for emergency use.

C. When the test article may be eligible for emergency use, RSS Specialist guides the physician/investigator to the COM-R RSS form *Notification of Emergency Use of a Test Article* and the COM-R RSS *Emergency Use* informed consent template form on the RSS website or IRBNet Library Manager.

D. RSS staff also alerts an IRB Chair or designee of the impending submission.

4.13.7.10. The Clinician Must Submit the Following:

A. COM-R RSS form *Notification of Emergency Use of a Test Article*;

B. Informed consent document; or

C. If the physician/investigator ascertains that informed consent cannot be obtained prior to administration of the test article, the physician/investigator:

- Attests on the UIC RSS form *Notification of Emergency Use of a Test Article* that the four conditions in 21 CFR 50.23(a) apply; and
- Has a physician who is not otherwise participating in the clinical investigation complete the COM-R RSS form *Independent Physician Certification: Emergency Use of a Test Article Without Informed Consent,* or
- If immediate use of the test article is required to preserve the subject's life and time is not sufficient to obtain an independent physician's determination, the physician/investigator makes the determination himself/herself and, within five business days after the use of the article, has the determination reviewed and evaluated in writing by an independent physician and submits this determination to the IRB.

D. Investigational Drug Brochure (*if available*);

E. Treatment Protocol (*if available*); and

F. Authorization from the sponsor to allow use of the test article by the physician/investigator or an approved IND/IDE or letter verifying exemption of IND/IDE from the FDA.

4.13.7.11. RSS Duties:

Upon receipt of the Emergency Use Application and supporting documents, RSS staff conducts a pre-review to ensure that the submission is complete and all necessary documentation is included. RSS staff then provides the submission and Emergency Use of a Test Article review guide to the IRB Chair, Chair's designee or RSS Director.

4.13.7.12. The Chair or Designee Duties, and RSS Specialist Documentation:

The Chair, designee or RSS Director reviews the submission to determine whether the request qualifies for emergency use under 21 CFR 56.102(d). The Chair or designee completes the review guide, and provides one of the following terminations:

A. Acknowledge based on information provided by the physician/investigator that the proposed emergency use meets the requirements of 21 CFR 56.102(d) and, when applicable, the requirements of 21 CFR 50.23(a) for exception from informed consent.

B. Modifications or additional information are required.

C. Proposed use does not qualify as emergency use.

D. After making a determination, the Chair returns the completed review guide and all documents to RSS Specialist. The Specialist then processes the submission as follows:

E. Draft approval letter and date stamp the informed consent document. The stamp used for HIPAA Authorizations is used, since the document is used only once and no expiration date is needed.

F. Uploads the date stamped documents and approval letter into the IRBNet study packet.

G. Contacts the physician/investigator via phone or e-mail when the letter and consent documents are ready for pick-up.

H. Faxes a copy of the determination letter to the facility where the procedure will be executed.

I. The IRB is notified of the emergency use by the inclusion of the event on the next convened meeting agenda.

4.13.7.13. Five-Day Follow-Up Report:

The physician/investigator must submit the COM-R RSS form Five-Day Follow-Up Report of Emergency Use of a Test Article to the IRB within five days of administration of the test article. In the *Five-Day Follow-Up Report of Emergency Use of a Test Article* form, the physician/investigator must also inform and provide documentation to the IRB of any exceptions to the requirement for informed consent if this was not done at the time of notification. The previously submitted *Notification of Emergency Use of a Test Article* form and any information listed in step 2 that was not provided with the *Notification of Emergency Use of a Test Article* form should also be submitted.

4.13.7.14. IRB Review of Emergency Use Application:

The IRB reviews the initial emergency use notification, five-day follow-up report, informed consent document, and any other information provided by the physician/investigator at the next available meeting. The IRB Chair or designee serves as the primary reviewer. The IRB determines if the criteria for an exemption from IRB review and, when applicable, the exception for the requirement of informed consent are met, and whether there are any further issues related to the treatment of the subject. The IRB's determinations are documented in the meeting minutes and communicated in writing to the physician/investigator. The follow-up report and IRB communication are added to the protocol file.

The acknowledgement informs the physician/investigator that the exemption from IRB review and approval allows for one emergency use of a test article without prospective IRB review at an institution. Any subsequent use of the test article at the institution requires prospective convened IRB review, and the physician/investigator should evaluate the likelihood of similar need for the drug, biologic or device. If future use is likely, the physician/investigator should promptly prepare and submit a protocol and initial review application for submission for convened IRB review.

4.13.7.15. Failure to Notify the IRB:

Failure to notify the IRB prior to emergency use of the test article, provide a five-day follow-up report to the IRB, or meet the requirements of 21 CFR 56.102(d) for emergency use or 21 CFR 50.23(a) for exception of informed consent is considered non-compliance and is evaluated by the IRB as described in the COM-R HSPP policies, including but not limited to, *Handling Complaints and Allegations of Potential Non-Compliance with Human Subject Protection Regulations, Reporting of Unanticipated Problems, Suspensions, Terminations, and Non-Compliance.*

References:

21 CFR 50.23(a)-(c), 21 CFR 56.102(d), 21 CFR 56.104(c), 21 CFR 312.36, 21 CFR 812.35(a)(2),
21 CFR 812..150(a)(4)
38 CFR 16.107(f)15.j
VHA Handbook 1200.5 (14)
FDA, Emergency Use of an Investigational Drug or Biologic, FDA Information Sheets, 1998 Update.
FDA, Frequently Asked Questions about Medical Devices, Information Sheet Guidance for IRBs,
Clinical Investigators, and Sponsors, January 2006.
FDA Guidance on IDE Policies and Procedures, dated January 20, 1998.

4.13.8. Humanitarian Use Device (HUD).

A device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year.

HUMANITARIAN USE DEVICE EXEMPTION (HDE): Food and Drug Administration (FDA) approval of an HDE permits the marketing of an HUD, subject to restrictions on charges and use. Specifically, HUDs cannot be sold for profit, except in the limited circumstances when indicated for use in children, and can only be administered in facilities after IRB approval is obtained, except in certain emergencies. Approval of an HDE requires evidence of safety and probable benefit but does not require establishing effectiveness.

. In order for a HUD to be used in treatment or diagnosis at COM-R, the HUD must have an approved HDE from the FDA and IRB approval. FDA regulations and COM-R HSPP require initial IRB review and approval at a convened meeting. Emergency and compassionate use of a HUD may be allowed in accordance with FDA regulations and COM-R HSPP policy.

Informed consent is not required by FDA regulations when a HUD is used for an approved indication, unless the use represents a clinical investigation. However, the COM-R IRB generally invoke their regulatory discretion in this circumstance and require documented informed consent. In lieu of the COM-R HUD informed consent template, health care practitioner (*investigator*) may request the use of an alternative format, e.g., substitution of the FDA approved patient information packet for some of the required sections of the COM-RHUD consent template.

Collection of safety and effectiveness data to support a premarket approval (PMA) application by the HDE- holder for the HDE-approved indication may occur under the HDE without the need to obtain an investigational Device Exemption (IDE). However, the activity is considered a clinical investigation (i.e., research) rather than clinical practice and, as with other FDA-regulated clinical studies, IRB approval and informed consent are required. Also, since the activity is now considered research, authorization from the patient (or waiver of authorization) under the HIPAA Privacy Rule is required for protected health information to be used or disclosed.

4.13.8.1. Application to IRB.

The health care practitioner (*investigator*) is required to submit the following materials to the IRB for review and approval of the use of a HUD:

A. COM-R HUD application;
B. FDA HDE approval order (*a list of approved HDEs along with the approval order, summary of safety and probably benefit, labeling and patient information is available at*):
   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2
C. Professional labeling;
D. Summary of safety and probable benefit;
E. Device manual or brochure (*if available*);
F. Patient labeling/Information Packet (*if available*);
G. Protocol (*if available*);
H. Consent form for use of the HUD.

The entire board receives copies of items A, F and H, while all items are provided to the primary reviewers. All IRB members have access to the complete protocol file, containing items A through H.

4.13.8.2. Consent for Clinical Use of the HUD.

A. Informed consent and documentation of informed consent is required when treating or diagnosing a patient with a HUD.

B. The format, required sections and recommended language for the HUD consent for clinical use are provided on the COM-R HUD consent template.

C. When FDA-approved patient information labeling or packet is available, this document may substitute for certain required sections of the COM-R consent, including "Why does my doctor want to use this . . .", "What will be involved with use of the HUD", "Risks", "Benefits", and "Alternative."

D. When available, any FDA-approved patient labeling information prepared by the manufacturer is to be provided and reviewed with the patient prior to use of the HUD regardless of whether it is being used as part of the consent process. The plan for how this will be conducted is to be described in the COM-R HUD application.

4.13.8.3. Initial IRB Review of a HUD.

A. Initial review of a HUD is performed at a convened meeting of the IRB.

B. IRB reviews the material listed in I. in making their determination.

C. IRB review and approval of the HUD request follows the review criteria at 21 CFR 56.111 as much as possible, including:

1. Evaluating the risks described in the product labeling and ensuring the risks are minimized,
2. Ensuring risks are reasonable in relation to the anticipated benefits of the proposed use of the device,
3. Ensuring informed consent is obtained from each prospective patient or their legally authorized representative,
4. Ensuring informed consent is appropriately documented, and
5. Where appropriate the plan for use of the HUD adequately monitors the safety of subjects.

D. IRB must verify that proposed use of HUD corresponds with the current labeling and does not exceed the scope of the FDA-approved indication.

E. The IRB evaluates whether the health care provider(s) is qualified through training and expertise to use the device.

F. The IRB may approve use of the HUD without any restrictions beyond the FDA-approved labeling or may impose more stringent criteria for use of the HUD as deemed necessary to provide additional protections.

G. IRB determines the continuing review frequency (*i.e., at least annually*) and whether it may occur by expedited procedures.

H. The IRB's determination is documented in the meeting minutes.

I. Use of the HUD should be restricted to personnel listed on the HUD application reviewed and approved by the IRB.

J. The HUD must be stored in a secure manner and labeled appropriately to prevent the use by unapproved personnel or the use of the device in an unapproved manner.

4.13.8.4. Continuing IRB Review of a HUD.

A. The IRB will conduct a continuing review of the use of the HUD at intervals appropriate to the degree of risk, but no less than once a year.

B. Continuing review may be performed by expedited procedures by the IRB Chair or member designated by the Chair.

C. Continuing review of the HUD should follow COM-R Continuing review policy. HUD-specific information that should be provided the IRB reviewer includes:

1. Number of times the HUD has been used;
2. Any problems associated with its use,
3. Unanticipated problems, including serious adverse events and deviations since the last review.
4. Any use outside of the FDA-approved labeling or emergency use.
5. Any information provided to the sponsor or FDA concerning use at other sites or any annual reports to the FDA, and
6. Any Medical Device Reporting reports or UIC Prompt Reporting reports.

4.13.8.5. Modifications to the HUD:

Modifications to the HUD or proposed changes to the clinical use of the device must be submitted for IRB review and approval using the UIC Amendment application. The amendment application should be accompanied by:

1) the FDA's approval of the modification,

2) the HDE holder's amendments to the HUD product labeling, clinical brochure, and/or other pertinent materials corresponding to the requested modification(s), and

3) the revised clinical consent form with the modifications indicated.

Collection of Safety and Effectiveness Data when HUD is used in Accordance with its Approved Indication(s).

A. Collection of safety and effectiveness data to support a PMA application by the HDE-holder for the HDE-approved indication may occur under the HDE without the need to obtain an investigational Device Exemption (IDE).

B. This activity is considered by the FDA to represent a clinical investigation (*i.e., research*) and, as with other FDA-regulated clinical studies, IRB approval and informed consent are required.

C. The investigator should submit the materials described in I. for IRB review and approval.

D. The investigator must also complete and submit the additional sections on the HUD application and Consent Form designated for completion when safety and effectiveness data are being collected for an FDA-regulated clinical investigation or other research activity.

E. Also, since the activity is now considered research, authorization from the patient (*or waiver of authorization*) under the HIPAA Privacy Rule is required for protected health information to be used or disclosed. HIPAA authorization language is incorporated into the COM-R HUD consent form.

F. Initial and continuing review by the IRB will follow the criteria in the COM-R Initial and Continuing Review Biomedical Review Guide .

G. Even when the data will not be submitted to the FDA, the collection of safety and efficacy related to use of the HUD for its approved indication by the investigator for activities meeting the OHRP or FDA definition of human subject research (*see COM-R HSPP policy Institutional Authorization for Determining whether Research or Other Activities Represent Human Subjects Research*) must follow the additional submission and review requirements described here for those activities representing FDA-regulated studies.

4.13.8.6. Considerations for Prompt Reporting.

A. Whenever the physician or health care provider primarily responsible for use of the HUD at COM-R becomes aware of information, from any source, that reasonably suggest that a HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider must report such findings to the FDA and the COM-R IRB as soon as possible, but not later than 10 working days after the Investigator first learns of the effect or problem. The COM-R Prompt Reporting Form should be used to submit this information to the IRB.

B. The reporting requirements outlined in the COM-R HSPP policy Unanticipated Problems and Other Events Requiring Prompt Reporting, should be adhered to with the use of the HUD.

C. The health care practitioner responsible for use of the HUD shall report any FDA actions regarding the HUD to the IRB within 10 working days of being notified.

D. Use of a HUD in an Emergency. The HUD may be used off-label (*i.e., a non-approved indication*) or without prior IRB approval in an emergency situation. The COM-R Policy on "Emergency Use of Test Article" must be followed, including obtaining concurrence of the IRB chair or designee, informed consent from subject or legally authorized representative, independent assessment from an uninvolved physician and authorization from the HDE holder.

E. Compassionate Use of HUD. The FDA allows the use of a HUD in circumstances

where the device is the only option available for a patient faced with a serious or life-threatening condition that does not meet the criteria of an emergency. A use is commonly referred to as 'compassionate use". Unlike emergency use, prior FDA approval is required before compassionate use occurs. As a first step, the clinician should seek the approval of the HDE holder and provide them with the following information:

1) Description of the patient's condition and circumstances necessitating
2) Discussion of why alternative therapies are unsatisfactory, an identification of any deviations from the approved HUD labeling required to treat the patient and patient protection measures that will be followed. The HDE holder must then submit an IDE (HDE) supplement to the FDA for approval. Once FDA approval is obtained, the investigator should submit the materials listed in I. along with documentation of FDA approval of the compassionate use to the IRB for review and approval.

References:

21 CFR 814 subpart H
21 CFR 803.30
21 CFR 814.124(a)
21 CFR 812.35
FDA Guidance: Draft Guidance for HDE Holders, IRBs, Clinical Investigators, and FDA Staff – HDE
Exemption Regulation: Questions and Answers, dated August 5, 2008.

4.14. Industry Funded Research – IRB Charges:

Charging industry sponsors for their share of the costs associated with the IRB review process allows COM-R to continue to provide the level of service required by our faculty. This practice is consistent with practices at the majority of research universities. Therefore, RSS charges an administrative fee for the IRB review of all industry sponsored human subject research.

A. Protocol Processing Fee Structure:

These fees apply only to industry sponsored research involving human subjects. Research involving human subjects supported by federal, foundation, division, or department funds will not incur these fees. The amount of all fees will be reviewed annually by the COM-R Accounting Department and are subject to change.

Review Type	Fee
Convened Review	$2,000.00
Expedited Review	$1,500.00
Exempt Review	$750.00
Continuing Review	$500.00

B. **Budget Preparation:**

All PIs submitting industry sponsored human subject research protocols to RSS are strongly encouraged to include a line item in the clinical trial agreement/study budget for the IRB review fees. Facilities and University administrative costs (*i.e., indirect cost, ICR, and F&A*) will not be applied to the IRB review fees. Payment of these IRB review fees is considered a contractual obligation of the sponsor.

C. **Payment of Protocol Processing Fees:**

These processing fees are assessments of real costs associated with protocol review by the IRB and are charged regardless of IRB approval or eventual project funding status. The PI is billed by the COM-R Accounting Department at the time of submission for initial or continuing review.