9.1 TYPES OF IRB SUBMISSIONS

Before an investigator may initiate any research activity that involves human subjects, the investigator is required to obtain either approval from the IRB for the research activity or obtain a determination that the research is exempt from the requirement of IRB review and approval.

Definitions:

Human subject: A living individual about whom an investigator conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Research: A systematic investigation designed to contribute to generalizable knowledge.

A. Non-Human Subjects Research

The IRB may determine that an activity does not meet the criteria for research involving human subjects as defined in the federal regulations at 45 CFR 46.102. "Projects that do not involve "human subjects" and/or are not considered "research," as described above, do not require review by the IRB. Submissions determined not to meet both criteria will be issued a "Not Human Subjects Research" determination and letter.

Research involving coded or de-identified private information or specimens is considered non-human subjects research when the private information or specimens cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

OHRP does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(e) if the following conditions are both met:

i. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

ii. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

   a. the investigators and the holder of the key entered into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);

   b. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

   c. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

*Note that information associated with a specimen that is coded according to the standards above (per OHRP guidance) may not necessarily meet the definition of de-identified under the HIPAA Privacy Rule. For example, if the code is derived from a patient identifier or certain data elements, such as dates of service or zip codes, the use or disclosure of the information

for research may still require HIPAA authorization or waiver of authorization, or, if the information constitutes a "limited data set," a data use agreement with the recipient of the information. Non-human subjects research does not require an exempt determination by the IRB as it does not constitute research involving human subjects as defined in CFR 46.102(e)).

Investigators who have questions related to this policy, such as what is considered identifiable information or are unsure of whether their research involves human subjects, should contact ORIC for guidance.

Note: this policy does not apply to human embryonic stem cells.

B. Case Reports

Case reports may or may not be considered research. A starting point is to consider whether the case report contains the elements of research (i.e., it specifically involves a *systematic investigation* with the intent to contribute to *generalizable knowledge*).

Simply summarizing an interesting treatment, presentation, or outcome of a patient, does not constitute research. Typically, when a case report is presented to share information for medical educational purposes or to request advice from colleagues on the clinical care of a patient or group of patients during a departmental meeting, conference, or other accepted venue for discussion of clinical management, it would not be considered a research activity and does not require IRB approval. However, when the intent is to evaluate a specific hypothesis (e.g., a hypothesis is generated in advance of a retrospective records review), this activity constitutes research.

ORIC staff is available to assist with the determination if a case report/case series meets the definition of human subjects research and requires IRB review. If requested, ORIC staff may provide a letter documenting the determination that the case report/case series did not meet the definition of human subjects research and does not require IRB review. To obtain this letter from ORIC, a completed Initial application in the electronic IRB system for the Case Report/Case Series .

It should also be noted that case reports must always be prepared in accordance with the requirements of the HIPAA privacy rule. Any access to or disclosure of Protected Health Information (PHI) in the case report must be done with the patient's authorization or, if the patient is deceased, authorization of the patient's family. If no PHI is disclosed, this does not apply.

C. Human Embryonic Stem Cells

Due to the ethical and moral implications surrounding the field of embryonic stem cell research, ORIC and the IRB have adopted this policy for proposals involving this area of research. The NIH defines "human embryonic stem cells (hESCs) as "pluripotent cells that are derived from early stage human embryos, up to and including the blastocyst stage, are capable of dividing without differentiating for a prolonged period in culture and are known to develop into cells and tissues of the three primary germ layers." Prior to beginning any work with hESCs, PIs are required to submit their proposals to the IRB for review. The IRB Chair, in collaboration with the Director of ORIC, will determine whether the project is considered exempt, or if expedited or full board review is warranted. An Investigator cannot make this

determination. When submitting a proposal involving the use of embryonic stem cells, the following items are required:

i. Initial Application in electronic IRB system:

a. Justification for exempt status based on the exempt status categories as defined in 45 CFR 46.104.

b. Identification of the clinic that will supply the embryos and obtain a copy of all clinical informed consent documents. If the clinic is affiliated with an academic institution, the IRB approval documents and Federalwide Assurance (FWA) number is to be provided.

c. Description of how the embryos will be obtained, and whether they are considered donated or discarded. The clinical informed consent document must contain information regarding donation of embryos to research. In Vitro Fertilization (IVF) clinic consent forms are to inform the donors regarding any use of their donated or discarded embryos for research purposes.

d. Documentation that the clinician at the IVF clinic has agreed to donate the embryos for use in the research project(s).

e. ESCRO Committee Review: In addition to the above requirements, the PI must submit the proposal to the Northwestern University Embryonic Stem Cell Research Oversight (ESCRO) committee for their review.

D. Human Subject Research

The IRB must review and approve all research involving human subjects.

The three levels of review include exempt, expedited, and full board review. For each submission ORIC requires the appropriate application completed in the electronic IRB system.

i. Application for IRB Exemption

Under the federal regulations, certain types of research are exempt from IRB review. Exemption from IRB review does not imply that an investigator is free from the ethical responsibility to human subjects who are part of the research; it signifies only that IRB review and (continuing) approval of the research is not required by federal regulations. The investigator is not permitted to make an exempt determination for their human subjects' research; instead, the investigator is required to submit a study using an Initial application in the ,electronic IRB system. This application outlines the criteria used for determining whether a study qualifies for an exempt determination. If the reviewer determines that a study meets the criteria, a letter is sent to the PI informing them of the determination and responsibilities.

ii. Initial Submissions for Expedited or Full Board Review

All Institutional investigators proposing to initiate a research activity involving human subjects must submit an Initial application in the electronic IRB system. The ORIC and IRB review under expedited and full board is a comprehensive evaluation of a research project that determines whether it is ethical to involve human beings as subjects based on the criteria for approval listed in federal regulations 45 CFR 46.111 and 21 CFR 56.111.

Research investigators and department heads will consider whether the research will involve human subjects as defined in 45 CFR 46.102. The research investigators may then submit to ORIC any research protocols that involve human subjects for a determination.

The Initial application submission in the electronic IRB system should contain all required protocol documents, including the following in the electronic IRB system:

a. Protocol: If the research activity is occurring at multiple sites, a multi-center protocol may exist. A full study protocol is to be uploaded if the convened IRB needs to review the application.

b. The Investigational brochure (IB) and/or previous data on the investigational agent for study under a new drug application (IND) 21 CFR 312.23(a)(5) and 312.55). For investigational devices, technical information, such as product inserts, manuals, and instructions for use, and other relevant material to evaluate the risk determination of the device. In addition, the IND/IDE letter issued from the FDA is also to be uploaded into this application.

c. Parental permission, adult consent, and adolescent assent forms: See the section 11 of the Policy and Procedure manual for more information about obtaining informed consent.

d. Research Safety Reviews:

   - A letter from the Radiation Safety Committee (RSC) is required to be uploaded into the Initial application when the research involves administration of radiopharmaceuticals or radioactive materials when the radioactive drug is experimental or is administered for research purposes only. If the research uses ionizing radiation without direct clinical indication, this also requires RSC approval.
   - A letter from the Institutional Biosafety Committee (IBC) is required to be uploaded into the Initial application if the research involves recombinant or synthetic nucleic acid molecules (r/sNA) molecules and biohazard agents.

e. Recruitment Material: any material that will be distributed to subjects or publicly posted containing information about the study is to be uploaded into the application. Documents will be reviewed and approved as part of the initial review. After a study is initially approved, new recruitment materials added will need to be submitted via a Modification application in the electronic IRB system.

f. Study Questionnaires, Surveys, and Diaries: any surveys, questionnaires, or diaries, which will be utilized in the research, are to be uploaded into the application.

iii. Renewal Submissions

Periodic review is required for ongoing research protocols at intervals appropriate to the degree of risk. The frequency and extent of periodic review for each study is based on the nature of the study, the degree of risk involved, the novelty of the research procedures, and the vulnerability of the study subject population. After a careful consideration of each of these factors, each protocol is assigned an approval period, after which it must be reviewed by the IRB.

Some research does not require annual review, and the IRB reviewer will document this per study. The IRB reviewer may request annual review and will document the protocol specific reasoning for this requirement. Reasons may include but are not limited to:

- Study staff Conflicts of Interest
- Risk to study population
- Study design
- Non-compliance

Studies not required to submit annually to the IRB will be issued a 3-year approval period. During this time, the PI and study team must still:

- Ensure all personnel comply with their HSR/GCP education requirements
- Submit any modifications to the study to the IRB for review prior to implementation
- Promptly report any Unanticipated Problems/Adverse Events/Protocol Deviations to the IRB for review
- Submit a Closure when the study is complete

Upon expiration of the 3-year approval period, if the study is still open and active, a Renewal must be submitted to the IRB for review.

Each IRB approval notice designates a period of time during which activities involving human research subjects may be undertaken. No research project may continue to recruit, enroll, or treat subjects or analyze data after the expiration date of the IRB approved research unless the IRB finds an overriding safety concern or ethical issue such that it is in the best interest of the participants to keep participating. Continuation of the research after midnight on the date of expiration of IRB approval is a violation of federal regulations.

To assist an investigator in fulfilling the requirement for Renewal, the investigator receives at least one notice from ORIC notifying them of the upcoming expiration date.

The IRB performs periodic review in order to monitor previously approved research to document that the protocol continues to protect sufficiently subject safety and welfare. A second objective of periodic review is to confirm that all information presented to subjects is complete, accurate, and up-to-date.

To fulfill this function, IRB requires that each investigator complete a Renewal application in the electronic IRB system, which provides a summary report on the progress of the research to date, including, but not limited to, the following:

a. A summary that contains relevant information required to determine whether the proposed research continues to meet the regulatory criteria for approval;

b. The number of subjects enrolled at the Institution and at all sites (if applicable);

c. Description of any adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research that were not previously reported;

d. Any recently published literature, new findings, or other relevant information; especially new information about risks associated with the research that may affect the subjects' willingness to continue participation;

e. A copy of the current stamped informed consent documents; and

f. Any relevant multi-center trial reports (data safety or clinical research organization monitoring reports).

As in their initial review, the IRB must evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of subjects' privacy and data confidentiality, safety monitoring procedures, and additional protections for vulnerable populations in order to determine the research continues to meet the criteria for approval outlined in 45 CFR 46.111 and 21 CFR 56.111.

iv. Modification Submissions

Amendments to approved research studies must be submitted to the IRB via a Modification application in the electronic IRB system, with both annotated and clean versions of revised documents. The IRB approval will indicate if it is necessary for active participants to be re-consented with the revised informed consent form. Please see IRB Policies and Procedures Manual Section 11 for more information on the requirement of re-consent/assent.

Proposed changes may not be implemented until the IRB has reviewed and approved the Modification, except when the changes are necessary to eliminate immediate hazards to subjects. In this case, the Modification must be submitted to the IRB within 72 hours and include the reason immediate action was taken. These changes will be reviewed by the IRB to determine if this was appropriate and consistent with ensuring the continued welfare of participants.

Note: Information on significant new findings that present potential of an increase in risks to participants (i.e., revised investigational brochure, protocol, etc.) or identify new risks are to be provided to active research participants immediately and their willingness to continue to participate confirmed. This communication should be well documented. As above, once the IRB reviews and approves the Modification and consent forms, active participants should be formally re-consented.

v. Unanticipated Problems and Adverse Event Reporting

Investigators are required to submit reports of all serious and unexpected adverse events experienced by human subjects that meet the criteria for reporting. These are to be submitted via an Incident Report in the electronic IRB system. Please refer to the Section 13 Data Safety Monitoring and Regular Reporting Requirements.

vi. Other Submissions

Any information relevant to the participation of human subjects in a proposed or approved research project in which the Institution (including its employees or physicians) is engaged should be submitted for review and if appropriate for review by the IRB. Examples of relevant materials include, but are not limited to documentation of temporary study suspension by the sponsor or PI, clarification of subject complaints, audit reports, study

drug shortages, or notice of FDA approval of study drugs or devices. In some cases, these materials may require consideration by the convened IRB. In each instance, the IRB will determine whether the new information should be relayed to enrolled subjects.

vii. Study Inactivation

Investigators are required to close the study with the IRB once all study activities have been completed to terminate the IRB approval. Research studies may not be inactivated if any of the following are true:

a. Enrollment, research-related interventions, and/or participant follow-up at the Institution are ongoing;

b. Data analysis or manuscript preparation is ongoing and involves the use of, or access to, personally identifiable information or protected health information;

c. Biological specimens containing individually identifiable information are being maintained in a repository that has been approved as part of the study or upon which analysis or research is ongoing at the Institution (If specimens were transferred to a separate repository that has ongoing IRB approval, the study may be closed);

d. Permission from an external sponsor to close the study has not been received.

Investigators who wish to inactivate their studies with the IRB are to submit a Closure application via the electronic IRB system. Once the Closure has been approved by the IRB, study records must be kept for:

e. 3 years post inactivation per Institutional policy;

f. 2 years post drug/device approval or program closure per FDA policy (21 CFR 312.57);

g. As specified by the study contract or as stipulated by the study sponsor

For all studies where consent was not obtained and private health information was collected, study databases should be de-identified and any correlation tools that link the de-identified data to the identifying information should be destroyed.

9.2 TYPES OF IRB REVIEW

A. Administrative Pre-Review

Research Compliance Coordinators (RCCs) conduct administrative and regulatory reviews of all submissions (Initial applications, Renewals, and Modifications), prior to forwarding the submission to the IRB Chair/Vice Chair or IRB for consideration. The review evaluates the submission for completeness and compliance with federal regulations, Institutional and ORIC policies, including IRB policies and procedures to minimize situations where time and effort are spent considering submissions that do not meet the regulatory criteria for IRB approval. As part of this process, the RCC works with research staff to update and modify submissions with the goal of addressing all regulatory and Institutional requirements. As needed, additional consultation may be sought from the IRB Chair(s), designated members, or others having expertise with the issues identified.