Collaborative Research and External IRB Review

1.0 Purpose

The purpose of this policy is to describe the requirements and procedures for collaborative human subject research in which the Wright State Institutional Review Board (IRB) acts as the Reviewing IRB for an external organization/investigator or for research in which Wright State University cedes its review to an external IRB.

2.0 Scope

This policy applies to all human subject research that is conducted by Wright State University (Wright State) faculty, staff and students and human subject research for which the IRB acts as the Reviewing IRB for an external entity via a reliance agreement.

This policy does not apply to human subject research conducted solely (e.g., Wright State will not be named in any publications/presentations and the research does not involve Wright State information, facilities or funding) by Premier Health or the Dayton Veterans Affairs Medical Center (Dayton VAMC) for which either organization has decided to cede review to an IRB other than the Wright State IRB. Use of non-Wright State external Reviewing IRBs for Premier Health or the Dayton VAMC will be governed by their respective institutional policies/requirements.

The only exception to this is human subject research conducted via the Clinical Trials Research Alliance (CTRA). Wright State University is considered to be "engaged" in all research conducted via the CTRA and therefore, the requirements of this policy apply to that research regardless of the location of the conduct of that research.

3.0 Definitions

3.1 **Central IRB** means an institutional al review board that specializes in reviewing specific type(s) of multi-site human subject research or is established to review projects funded by a specific agency. For example, the National Cancer Institute Central IRB reviews projects sponsored by the National Cancer Institute.

3.2 **Director** means a member of the HRPP Office who directs, manages, implements, and administers policies and procedures related to research involving human subjects. The Director provides for all compliance and

regulatory functions of the IRB ensuring adherence to all federal, state, and local regulations and policies governing research involving human subjects including the Belmont Report and the requirements set forth in Title 45, Part 46 of the Code of Federal Regulations.

3.3 **Engaged** means involved in human subject research in such a way that the ethical and regulatory requirements for human subject protection are applicable. An individual (or organization) becomes engaged in human subject research when it receives a direct federal award to support the research and/or when an individual (or organization's employee or agent) obtains the following:

3.3.1 Data about research subjects through intervention or interaction
3.3.2 Identifiable private information about research subjects
3.3.3 Informed consent of research subjects.

3.4 **Federalwide Assurance (FWA)** means a formal, written, binding attestation in which an institution ensures to the U.S. Department of Health and Human Services (HHS) that it will comply with applicable regulations governing the protection of human subject.

3.5 **Human Research Protection Program (HRPP)** means a multi-tiered program involving the University administration, the Wright State Institutional Official, the Wright State Institutional Review Board, HRPP Office, other research administrative and compliance offices, and investigators.

3.6 **Individual Investigator Agreement** means a written agreement between Wright State University and a collaborating external investigator who will be engaged in Wright State human subject research that describes each party's responsibilities for research conduct and oversight.

3.7 **Institutional Official (IO)** means a high-level official who is the signatory on the Federalwide Assurance (FWA) filed with OHRP and has the authority to represent the institution. The Vice Provost for Research serves as the IO for Wright State University.

3.8 **Institutional Review Board (IRB)** means a committee established to review and approve research involving human subjects. The purpose of the IRB is to ensure that all human subject research be conducted in accordance with all federal,

institutional, and ethical guidelines.

3.9 **Multi-Site Research Study** means a study that uses the same protocol to conduct non-exempt human subjects research at more than one site.

3.10 **Office of Human Research Protections (OHRP)** means the administrative agency that oversees the United States' system for protecting volunteers in research conducted or supported by the U.S. Department of Health and Human Services (DHHS).

3.11 **Off-Site Research** means research performed at a location/site that is not owned by or under the direct control of Wright State University.

3.12 **Overall Principal Investigator** means the principal investigator with ultimate responsibility for the overall conduct, safety, regulatory oversight, and data integrity for a multi-center research study.

3.13 **Site Principal Investigator or Site PI** means the primary individual responsible for the preparation, conduct, and administration of a human subject research study at the relying site.

3.14 **Reliance Agreement** (also called an Authorization Agreement) means a written agreement between organizations collaborating in non-exempt human subject research that describes each organization's responsibilities for IRB review and oversight of research.

3.15 **Relying Organization** means the organization where the research will take place, and which will rely on the review of an external IRB which will serve as the Reviewing IRB for the research (usually a multi-site study). Sometimes the relying organization/IRB is also referred to as the relying site.

3.16 **Reviewing IRB** means the IRB that provides the ethical and regulatory review of the research for the Relying Organization.

3.17 **Sponsor** means any person or entity that takes responsibility for, initiates, or funds a study. The sponsor may be an individual, pharmaceutical company, device manufacturer, governmental agency, academic institution, private organization, or other organization.

4.0 **Policy**

The requirements of the Wright State HRPP apply to all research involving human subjects conducted on behalf of the University, regardless of funding or location. Research under the jurisdiction of the HRPP must be reviewed by the Wright State IRB unless a written reliance agreement is in place which appropriately cedes IRB review to an external IRB (i.e., Reviewing IRB).

It is important to understand that Wright State's reliance on an external IRB only transfers IRB review responsibilities to another entity to avoid duplication of effort regarding IRB review. Wright State and its investigators still maintain full responsibility for the conduct and oversight of that research (e.g., institutional review of investigator qualifications, financial disclosure, biosafety and other ancillary reviews), in addition to ensuring compliance with the terms of the Reviewing IRB approval. For this reason, Wright State requires submission of an abbreviated application (External Reliance Request Form) and institutional review and approval of that application prior to local study start. This institutional review is coordinated by the HRPP Director (Director) but it is not a "second" IRB review.

In certain situations, the Wright State IRB may serve as the Reviewing IRB for a collaborative research site and/or collaborative investigator engaged in Wright State research. The review and approval of this reliance will be managed via the normal new study submission process (i.e., Initial Review Form) in the electronic submission system. However, the Wright State IRB will not serve as the required single IRB (sIRB) for federally funded multi-site human subject research. Investigators involved in proposing such research should consult with the HRPP Office for further guidance.

It is also important to note that reliance agreements will only be executed for non-exempt human subject research. Wright State investigators must apply to the Wright State IRB to obtain an exemption determination regardless if a collaborating institution has already determined the research to be exempt. Likewise, Wright State will not provide exemption determinations for external organizations or individual collaborators, except for Premier Health and Dayton VAMC investigators, when requested.

5.0 **Procedures**

5.1 Local Collaborative Institutions Relying on the Wright State IRB

This section describes the master reliance agreements that are in place to foster collaboration between Wright State and its primary affiliated organizations. A master reliance agreement allows for ceded IRB review of all future reliance requests (or a certain subset of requests) without the need to negotiate a separate reliance agreement for each study. Additional master agreements may be negotiated by Wright State in the future. Therefore, investigators should consult the HRPP website list before initiating an external reliance request to see if a reliance agreement covering that research already exists.

5.1.1 Premier Health and Dayton Veterans Affairs Medical Center

Long-standing master reliance agreements are in place to allow the Wright State IRB to act as the Reviewing IRB for both Premier Health (includes Miami Valley Hospital, Upper Valley Medical Center and Atrium Medical Center) and the Dayton Veterans Affairs Medical Center (Dayton VAMC). These agreements were put into place as many Wright State Boonshoft School of Medicine investigators also hold staff appointments at these health care organizations and neither organization currently operates their own local IRBs.

Premier Health or Dayton VAMC investigators conducting studies via these master agreements should indicate this reliance in the Initial Review Form via the electronic submission system. It is important to understand that these master reliance agreements do not prevent Premier Health or Dayton VAMC from relying on other external IRBs for studies not involving Wright State University (see Section 2.0). However, if a study involves both Wright State University and Premier Health/Dayton VAMC, Wright State must also execute a reliance agreement with the external IRB to be able to appropriately cede its review requirements.

5.1.2 Wright State Physicians

Wright State Physicians (WSP) does not have a reliance agreement in

place to utilize the Wright State IRB. However, WSP investigators who are also faculty members in the Boonshoft School of Medicine can utilize the Wright State IRB for studies in which Wright State acts as the grantee or studies that are part of their faculty member responsibilities. Research conducted outside of the scope of a faculty appointment in which the funding is awarded directly to the practice must have an executed reliance agreement (see Section 5.2.2) in place for WSP to utilize the Wright State IRB as its Reviewing IRB for that study.

5.2 Single-Study Reliance on Wright State IRB for Collaborative Research

5.2.1 Collaborative Research Involving Multiple IRBs of Record

Wright State investigators applying to the Wright State IRB for collaborative research that also involves investigators from another organization who will be receiving review from their own IRB (e.g., University of Dayton) should not list those external investigators in their Wright State IRB new study submission. In such cases, each site PI will be responsible for complying with the terms of their own IRB approval and meeting the local requirements for investigator education and disclosure.

A reliance agreement is not needed for this type of collaborative research.

5.2.2 Collaborative Research in Which Wright State IRB Acts as Reviewing IRB

Wright State investigators applying to the Wright State IRB for research involving investigators from another organization (e.g., Miami University, University of Dayton) who want to rely on Wright State IRB review should list each external investigator in the personnel table and indicate the request for the Wright State IRB to act as the Reviewing IRB via the applicable questions in the Initial Review Form. Upon HRPP Office receipt of the application in the electronic submission system, the Director will initiate the reliance agreement or independent investigator agreement negotiation process with the applicable investigator/institution. This may involve contacting the Wright State PI for more information.

The Wright State IRB will only approve human subject research at off-site

locations for which the Wright State IRB has an understanding of the local research context and sufficient oversight mechanisms in place. The Wright State IRB will not review Health Insurance Portability and Accountability Act of 1996 (HIPAA) for organizations via an individual study reliance agreement. The Relying Organization must complete such reviews under their own HIPAA policies and procedures.

Normally, Wright State will only enter into reliance agreements with organizations that have an active Federalwide Assurance to ensure that standard human subject protections are in place. External investigator training and disclosure requirements will be dictated by the terms of the reliance agreement. In most cases, final approval for studies in which the Wright State IRB acts as the Reviewing IRB will not be released until Wright State receives a fully executed reliance agreement and the Wright State IRB completes its normal review and approval process.

Negotiating a reliance agreement may take several weeks or more, therefore the Wright State PI should plan the timing of his/her IRB application to ensure that there is enough time to meet other deadlines related to the research (e.g., grant submission deadlines). Investigators who need additional guidance about the reliance process for their study should contact the Director.

The Wright State PI (a.k.a., site PI) is responsible for collecting and reporting Relying investigator/Organization activities (e.g., subject recruitment, reportable event, etc.) as part of the normal submission process to the Wright State IRB during the conduct of the study. Wright State's electronic submission system is not structured to enable external sites to submit reports or receive approval notifications. Instead, the responsibility lies with the site PI to have a communication plan and designated study team members to manage it.

5.3 Individual Investigator Agreements for Independent Investigators

In limited cases, Wright State will agree to act as the Reviewing IRB for research involving an independent investigator that is not associated with an organization that has an IRB, a Federalwide Assurance or a master reliance agreement with Wright State. For example, a community physician who operates a private

practice may be allowed to participate in a Wright State research study based on completion of an Individual Investigator Agreement, Wright State credentialing and demonstration of adequate facilities and HIPAA compliance, when applicable. A Wright State investigator must act as the site PI for collaborative research involving an independent investigator.

5.4 Wright State Reliance on External IRBs

5.4.1 Types of External IRBs and Reliance Requirements

From Wright State's perspective, an external IRB is any non-Wright State IRB. It can be an accredited commercial, central, other academic, or hospital-based IRB. A central IRB is a board that specializes in reviewing a specific type of human subject research or is established to review projects funded by a specific agency. For example, Wright State has an agreement in place to rely on the NCI Central IRB for research sponsored by the National Cancer Institute.

A single IRB (sIRB) is defined as the IRB that is designated via negotiated terms and formal reliance agreements, to act as the sole IRB to conduct the initial, continuing and any subsequent review of a multi-site research project for all sites conducting the same research protocol. The requirement for sIRB review applies to all federally-funded awardees in the United States and all participating research sites within the United States, except for research funded by the Department of Justice.

Wright State will comply with the *National Institutes of Health (NIH) Policy on the Use of a Single Institutional Review Board of Record for Multi-Site Research* effective January 25, 2018 and the sIRB Common Rule requirements effective January 20, 2020, However, as stated above, Wright State will not agree to act as the sIRB for federally-funded research, but may participate in such research as a Relying Organization via the procedures outline in Section 5.5. It is also important to note that Wright State is not a member of the SMART IRB and cannot enter into reliance agreements via that program at this time.

Wright State's decision to rely on an external IRB for a study or a group of

studies will be based on, but not limited to, the following:

- Regulatory requirements (e.g., FDA, DHHS exemptions, HIPAA, NIH sIRB) and study risk level.
- Extent of procedures to be performed by local investigators
- Grant requirements, when applicable, and
- Qualifications of the external IRB, including presence of Reviewing IRB SOPs that include the following:
    - Procedures for conducting initial and continuing review of research and for reporting findings to investigator and research site.
    - Procedures for determining which studies require reviewing more often than annually and for determining that no changes have occurred since the last review and for ensuring prompt reporting of changes in research activity.
    - Procedures for ensuring that changes to approved research during the period when the study is currently approved may not be initiated without IRB review and approval, and
    - Procedures for prompt reporting to the IRB, appropriate institutional individuals and FDA/OHRP of unanticipated problems involving risks to human subjects or others; instances of serious or continuing noncompliance with regulation or IRB determinations; or any suspension or termination of IRB approval.

Once a decision has been made that the reliance is appropriate per the conditions above, a reliance agreement will be negotiated by the Director and then reviewed and signed by the Wright State Institutional Official.

5.4.2 Wright State Master Agreements with External IRBs

Wright State has several master reliance agreements in place for reciprocal review or for ceding review to an external IRB. These agreements describe each organization's responsibilities, including those for IRB review, reporting (e.g., unanticipated problems) and research oversight or refer to relevant SOPs/policies that describe how these

responsibilities will be met.

Currently, there are master agreements in place for:

- 88th Medical Group, Wright-Patterson Air Force Base IRB (Reciprocal Agreement)
- Air Force Research Laboratory, Wright-Patterson Air Force Base IRB (Reviewing IRB Only)
- Advarra IRB (Reviewing IRB Only)
- Dayton Children's Hospital IRB (Reviewing IRB Only)
- NCI Central IRB (Reviewing IRB Only)
- WIRB-Copernicus Group IRB (Reviewing IRB Only)

Wright State investigators who request to cede review to one of these external IRBs must indicate so in the External Reliance Request Form via the electronic submission system. Investigators are responsible for any costs associated with utilizing an external IRB and Wright State may disapprove a request to utilize an external IRB even though a master reliance agreement is in place. For example, if the external IRB does not have appropriate expertise to review a study involving a local context issue, the request may be disapproved (see Section 5.5 for more information about the review process).

5.4.3 Clinical Trials Research Alliance (CTRA) Research

Wright State is considered to be "engaged" in human subject research for all human subject research conducted via the Clinical Trials Research Alliance (CTRA) even though most CTRA research activities are conducted in local health care facilities. Master reliance agreements between Wright State, Premier Health and the commercial IRBs Advarra and Western IRB are in place for applicable CTRA studies, negating the requirement to negotiate reliance agreements for CTRA on a per study basis. However, all CTRA studies must still receive Wright State institutional review and approval prior to study start via the External Reliance Request Form and review process described in Section 5.5.

5.5 Wright State Review Process for Ceding Local IRB Review

The following sections define the specific steps required to obtain institutional approval to cede IRB review of Wright State human subject research to an external Reviewing IRB:

5.5.1 External Reliance Initial Submission

For each study, the principal investigator (PI)/regulatory coordinator must create a new study in the electronic submission system, select the External Reliance Request Form and complete and submit requested information. This form is meant to be an abbreviated application, in that less information is requested than required for regular IRB review. The information requested will:

- Facilitate training and credentialing review of all Wright State/affiliated hospital study team members that will be engaged in conducting that research
- Allow for identification of any local context issues
- Ensure completion of any required ancillary reviews, and
- Provide information needed for Wright State to complete any post-approval monitoring activities.

It is especially important for the PI/regulatory coordinator to provide accurate information about the proposed Reviewing IRB in the submission so that the Director can begin negotiating a reliance agreement or evaluating whether research is covered by existing reliance agreement. If the Reviewing IRB has already provided a draft reliance agreement to the PI/regulatory coordinator, he/she should attach the draft to the initial external reliance submission.

In certain circumstances (e.g., negotiating a master agreement before a specific study request is known), the Director may begin the reliance agreement negotiation process prior to the submission of the External Reliance Request Form.

It is expected that external reliance review submission packet will be returned to the PI/regulatory coordinator several times during the review

process so that he/she can update/add Reviewing IRB documents/approvals as they are finalized.

Before the reliance request can receive final written approval from the Director, the external reliance submission should include the following documents:

- Approved Informed Consent Forms, if applicable
- Approved Protocol Submitted to Reviewing IRB or equivalent
- Local Ancillary Review Approvals (i.e., Institutional Biosafety Committee, Environmental Health and Safety, Premier Health, Dayton VAMC), and
- Reviewing IRB Approval Letter or Equivalent

5.5.2 Reliance Agreement Review and Approval Process

Once the Director or the Director's designee has received the external reliance request, he/she will either confirm that the proposed research falls under the scope of one of the existing master reliance agreements or use the information provided by the Wright State PI/regulatory coordinator to contact officials at the Reviewing IRB to begin negotiating a new reliance agreement. In certain circumstances, the Director may decline the reliance request in writing and require that the Wright State investigator submit an application to the Wright State IRB.

Wright State currently utilizes template reliance agreements for both acting as the Reviewing IRB and the Relying Organization. However, the Director on behalf of Wright State can negotiate reliance provisions or utilize the Reviewing IRB's agreement when appropriate. Normally, review by the Wright State General Counsel's Office is required before a reliance agreement that does not utilize approved template language can be signed/executed by the Wright State Institutional Official.

A copy of the fully executed reliance agreement must be maintained in the electronic submission file for the study.

Reliance agreements must not be signed or negotiated by the Wright State PI or other study team members. Normally, no study activities may

move forward at Wright State until both the Reviewing IRB has approved the study and the Director has given final approval.

Once a complete submission application is received and approved by the Director, he/she will send a written 3-year approval letter to the Wright State PI/regulatory coordinator via the electronic submission system email notifying the study team that they are approved to start the study.

5.5.3 Required Amendment Submissions

The Wright State PI must submit an Amendment Form to request Wright State approval to add any local investigators to the study team after the date of the initial Wright State approval of the external reliance submission. This submission requirement is in addition to any Reviewing IRB requirement regarding personnel changes. When Reviewing IRB also requires formal review of personnel changes, Wright State investigators new to the study cannot be involved in any study activities until both approvals (i.e., Reviewing IRB and Wright State) are obtained by the PI/regulatory coordinator.

5.5.4 Reportable Events

The PI must submit a Reportable Event Form if an unanticipated problem or serious or continuing non-compliance occurs involving Wright State investigators. This reporting requirement is in addition to any Reviewing IRB's requirement regarding required reporting of events/unanticipated problems.

The Director will work with the PI, the Reviewing IRB, and applicable Wright State institutional officials to ensure that the event/problem is properly addressed. The Reviewing IRB is responsible for the formal IRB review of the event/problem and any required reporting to federal officials in accordance with its policies and procedures, unless otherwise stated in the executed reliance agreement.

5.5.5 Renewal of Wright State Reliance Approval Period

If the study will be conducted beyond the initial 3-year reliance approval

period, the PI must submit an External Reliance Progress Report via the electronic submission system at least six weeks before the reliance expiration date. This report must include a copy of the current Reviewing IRB-approved consent documents and protocol. It must also include information regarding local subject recruitment to date, a summary of all amendments to date, a summary of any subject safety related events or problems that occurred, and the plan to conduct the study locally during the next 3-year approval period.

The Director will review the Progress Report and send a written letter extending the reliance approval period, as appropriate.

5.5.6 Study Closure

The PI must submit a Study Closure Form in the electronic submission system when all approved investigators listed in the personnel table have completed all local research interactions/interventions and analysis of identifiable data. This must be done before the reliance expiration date. Once the form has been reviewed, the Director will send the PI the reliance closure letter via the electronic submission system.

5.6 Wright State Institutional Oversight and Investigator Responsibilities

Wright State investigators conducting human subject research under the Reviewing IRB approval are still responsible for ensuring that the safety, health, and welfare of the study subjects and their information/biospecimens are properly protected. They are also responsible for understanding and complying with the terms of the Reviewing IRB approval and following all applicable Wright State policies.

Wright State is responsible for taking actions to properly oversee the conduct of human subject research in which IRB review was ceded to an external entity. The external reliance submission review process is part of this oversight. Risk level, procedures performed, sponsor requirements and investigator conduct will determine which studies receive further review by Wright State via post-approval monitoring, quality improvement reviews, or formal audits.

5.7 Non-Compliance

Failure to comply with the requirements of this policy (i.e., reliance on external IRB without Wright State institutional approval) after its effective date may result in administrative actions and or non-compliance reporting to the Reviewing IRB, sponsors and federal agencies.

6.0 Records

IRB records for research that are subject to Department of Health and Human Services or Food and Drug Administration regulations, including meeting minutes, must be retained for at least three years after completion of the research that is the subject of the review and must be accessible for inspection and copying by authorized representatives from OHRP and/or FDA at reasonable times and in a reasonable manner (45 CFR 46.115(b); 21 CFR 56.115(b)).

The IRB minutes may have records pertaining to the review of multiple studies. Relevant portions of the minutes must be retained until the regulatory retention period for each study is satisfied. When Wright State acts as the Reviewing IRB, only sections of the minutes that pertain to the Relying Organization's study will be provided upon request to the Relying Organization.

All other records related to this policy will be stored and maintained in accordance with Wright State policy, federal regulations, and sponsor requirements associated with the human subject research under review.

7.0 References

7.1 45 CFR 46.114
7.2 21 CFR 50
7.3 21 CFR 56
7.4 FDA Cooperative Research Guidance
7.5 FDA Non-Local IRB Review Guidance
7.6 OHRP Engagement Memo
7.7 Using a Centralized IRB Review Process in Multicenter Clinical Trials