



THE UNIVERSITY OF
TOLEDO

Human Research Protection Program
Written Procedures

Federalwide Assurance #: 00010686

**Biomedical
Institutional Review Board**

**Biomedical Cancer
Institutional Review Board**

**Social, Behavioral and Educational
Institutional Review Board**

NOTICE REGARDING UPDATES TO THESE PROCEDURES

**The University of Toledo Human Research Protection Program
Written Procedures**

These procedures are updated periodically. The most recently updated version can be found on the Human Research Protection Program (HRPP) [website](#). You should access the website to ensure that you are reviewing the most current version of these procedures.

Table of Contents

I.	Definitions	6
II.	Eligibility to Conduct Human Subject Research.....	6
A.	Principal Investigator.....	6
B.	Student Research Projects	6
III.	Regulatory Compliance	6
A.	Federal Regulations	6
B.	Federal Regulatory Guidance	6
IV.	General Requirement for Review of Human Subject Research	6
A.	Responsibility for Review of Research	6
B.	Prior Review of New Research	7
C.	Prior Review of Changes to Research	7
V.	IRB Membership and Responsibilities.....	8
A.	IRB Membership	8
B.	Responsibilities of IRB Members.....	9
VI.	Application Requirements for IRB Review of Research	9
A.	Submission Deadlines	9
B.	Application Content for New Research.....	9
C.	Application Requirements for Continuing Review	10
VII.	IRB Review of Research	11
A.	Determination of Level of Review	11
B.	General Guidance Relevant to Initial and Continuing Review	11
C.	Expedited Review of Research.....	11
D.	Convened Review of Research.....	12
E.	Continuing Review of Research.....	15
F.	Verification of No Material Changes	17
G.	IRB Observation of Informed Consent Process	17
H.	Emergency Review of Convened Research.....	17
I.	Exempt Research	17
J.	Reporting IRB Actions to Investigators	18
K.	Reporting IRB Actions to University Officials	18
L.	Student Research Projects	18
M.	IRB Determination of Significant Risk vs. Non-Significant Risk Devices	19
N.	IRB Review of Humanitarian Use Devices (HUDs)	21
O.	Reporting Research Issues to the IRB, University Officials and Federal Authorities.....	22
P.	IRB Review of Adverse Events and Unanticipated Problems.....	26
VIII.	IRB Operations and Record Keeping	29
A.	Responsibility for Maintenance of Records	29
B.	IRB Records and Documentation	29
IX.	Investigator Responsibilities	31

**The University of Toledo Human Research Protection Program
Written Procedures**

X. Research Conducted Off-Campus or With a Non-UToledo Researcher.....32

- A. Investigator Responsibilities32
- B. Collaborative Research with Researchers or Institutions That Are Not Federally Assured 32
- C. Research Conducted in Collaboration with a Federally Assured Institution.....33
- D. Reliance on a Central or Independent Institutional Review Board33

XI. IRB Compliance Activities 34

- A. Compliance Responsibilities34
- B. Compliance Support Visits – Compliance Monitoring34
- C. Non-Compliance Reporting.....34
- D. Initial Review of Reports of Compliance Issues:35
- E. Compliance Oversight Review and Evaluation (CORE) Process36
- F. Convened IRB Review of Alleged Non-Compliance.....37
- G. Suspension or Termination of Research39

APPENDIX A: 45 CFR 46.111..... 41

APPENDIX B: Categories of Research That May Be Reviewed by the IRB through an Expedited Review Procedure43

APPENDIX C:46

Findings the IRB Must Make and Document to Approve an Alternative Consent Procedure46

List of Revisions

Final Version – July 18, 2007

Revisions – May 23, 2014

Revisions and Administrative Updates – April 28, 2020

- **Added Table of Contents and List of Revisions**
- **Updated office name from DHRP to HRPP throughout document**
- **Updated throughout document to reflect changes in the UToledo Protection of Human Subjects in Research Policy #3364-70-05, revised Aug. 19, 2019**
- **Added mention of Cancer Biomedical IRB throughout document**
- **Added and updated hyperlinks to federal regulations throughout document**
- **Updated language from federal regulations to reflect 2018 Common Rule changes throughout document, including Appendix A and C and sections related to continuing review of expedited research**
- **Added new or revised procedures approved in 2019**
 - **IV.C.2** – Added Single Subject Exception Procedure from Procedure for Reporting of Protocol Deviations, Violations and Exception Requests, which was approved and posted April 1, 2019
 - **VII.E-F** – Replaced these sections with updated versions from the Frequency of IRB Review; Verification Regarding Material Changes document, which was approved and posted on Sept. 12, 2019
 - **VII.O** – Added definitions and procedures for reporting research issues, excerpted from the Procedure for Reporting of Protocol Deviations, Violations and Exception Requests, which was approved and posted April 1, 2019 and the Adverse Event Procedure which was approved and posted April 1, 2019
- **Additional new or revised procedures**
 - **VII.D.2(b-g)** – Added a procedure for review of research at a convened meeting, definition of quorum, and procedure for calculating a majority, updated voting option language
 - **VII.E.1.d** – Added an Annual Progress Report procedure
 - **VII.N** – Added a procedure for IRB determination of significant risk vs. nonsignificant risk devices
 - **VII.N** - Added a procedure for IRB review of humanitarian use devices (HUDs)
 - **VII.O.1** – Added definitions related to the determination of reportable events
 - **VII.O.5** – Significantly revised procedure for reporting to university officials and federal authorities

**The University of Toledo Human Research Protection Program
Written Procedures**

- **VII.P** – Added procedure for IRB review of adverse events and unanticipated problems
- **X.D** – Added a procedure for reliance on a central or independent IRB
- **XI** – Significantly revised procedures for IRB compliance activities
- **Administrative updates to reflect university-level changes**
 - **V.A.4. and 5.** Revised to reflect change in appointing authority from the president / provost to vice president for research and duration of IRB member terms of service.
- **Non-substantive procedural revisions associated with transition to IRB Manager software – throughout document**
- **Corrected minor typographical errors throughout document**

**The University of Toledo Human Research Protection Program
Written Procedures**

PROCEDURES

These Procedures describe the required processes for obtaining institutionally and federally required approval to conduct *UToledo-Related Human Subject Research*.

I. Definitions

Words that appear in bold, italicized text are defined in Section D of the UToledo [Protection of Human Subjects in Research Policy #3364-70-05](#).

II. Eligibility to Conduct Human Subject Research

A. Principal Investigator

Any *research* involving *human subjects* must be under the supervision of a qualified principal investigator. UToledo policy ([#3364-70-05, Section E.2](#)) specifies that only university-salaried faculty, appropriately qualified salaried / contract university personnel or duly appointed community-based clinical or research faculty are eligible to serve as a principal investigator on a UToledo *IRB* study. Residents are considered to meet these eligibility criteria.

B. Student Research Projects

All students, including graduate students, conducting human subject research must have an appropriately qualified individual (as described in A above) listed as the principal investigator on their research application. The principal investigator must be in a position to provide human subject protections guidance, provide direct, personal, day-to-day oversight of activities and personnel associated with the study, and guide the student in compliance with UToledo research policies and *IRB* procedures (UToledo policy [#3364-70-05, Section E.2.a](#)).

III. Regulatory Compliance

A. Federal Regulations

In addition to compliance with DHHS regulations for the protection of human subjects at [45 CFR 46](#), when reviewing FDA-regulated research, the *IRB* also applies [21 CFR 50](#), Protection of Human Subjects, and [21 CFR 56](#), Institutional Review Boards. Clinical research involving FDA-regulated “test articles”, such as drugs, biological products, and medical devices is also reviewed under applicable FDA regulations; [21 CFR 312](#) (Investigational New Drug), [21 CFR 812](#) (Investigational Device Exemptions).

B. Federal Regulatory Guidance

The *IRB* relies heavily on current guidance documents published by OHRP for all research subject to regulation, as well as FDA Information Sheet Guidance for Institutional Review Boards with respect to clinical research. The current documents are available on the [OHRP](#) and [FDA](#) websites.

IV. General Requirement for Review of Human Subject Research

A. Responsibility for Review of Research

1. **Institutional Review Board (IRB):** The requirement for *IRB* review and approval of research involving *human subjects* is outlined in UToledo policy [#3364-70-05](#) and by federal regulations at [45 CFR 46](#) and for FDA-regulated products, [21 CFR 56](#). Since it

**The University of Toledo Human Research Protection Program
Written Procedures**

can be difficult to determine if a study requires IRB review, the IRB encourages researchers to submit the Not Human Subject Research form for review in order to receive a formal determination. The IRB has primary responsibility for review of *human subject research*.

2. **University Authority:** Although other university authority may prohibit a project that is approved by the IRB, university authority may not approve a project that is not approved by the IRB. Similarly, the UToledo president or other university authority may impose stricter limitations on the conduct of research than the IRB; however, no limitation placed by the IRB may be relaxed or overruled. ([45 CFR 46.112](#))

B. Prior Review of New Research

Federal regulations ([45 CFR 46.103.d](#); [21 CFR 56.103.a](#)), UToledo policy ([#3364-70-05](#)), and ethical guidelines require IRB review prior to beginning any research on *human subjects*. There is no emergency exception for beginning *research* without prior IRB review. Nothing in these procedures is intended to limit the authority of a physician to provide emergency medical care (see subsection 2 below), to the extent the physician is permitted to do so under applicable federal, state, or local law.

1. **No Retrospective Approval:** The IRB will not retrospectively approve *human subject research* that begins or occurs without IRB approval, or continues beyond the approval period. Researchers who obtain data through research without current IRB approval shall not use the data in a manner that represents the researcher had IRB approval to conduct the research.
2. **Emergency Medical Care:** A patient may not be considered a research subject under [45 CFR 46](#) when emergency medical care is initiated without prior IRB review and approval. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity.

C. Prior Review of Changes to Research

1. **Prior Approval of Changes:** Any changes to a research protocol, study documents or data collection tools that require IRB approval must be reviewed and approved by the IRB prior to implementing changes. Examples of changes that must be approved by the IRB include, but are not limited to, changes in research methods, data collection tools, *study personnel*, informed consent forms and recruitment materials.
2. **Single Subject Exceptions:** If a decision to depart from the approved protocol is under the control of the PI, and applies to only one subject (for example, delaying one subject's treatment due to lab results or other findings), the PI should as soon as possible submit a Single Subject Exception request to be reviewed and approved by the IRB prior to departing from the protocol, unless the decision is made to avoid an apparent immediate hazard as described in (3.) below.
3. **Emergency Situations:** Changes may be made to a research protocol without prior review and approval only where necessary to eliminate apparent immediate hazards to the human subjects, as described under [45 CFR 46.108](#) and [21 CFR 56.108](#). These emergency changes to a protocol must be reported to the IRB within 10 business days, unless the study involves an FDA-regulated device. Emergency deviations in device studies must be reported to the IRB within 5 business days ([21 CFR 812.150\(a\)\(4\)](#)).

**The University of Toledo Human Research Protection Program
Written Procedures**

V. IRB Membership and Responsibilities

A. IRB Membership

University faculty, university staff and members of the community are invited to serve on one of the three of the UToledo **IRBs**. Members with varied expertise and perspectives are needed to enable the **IRB** to conduct thorough reviews of the research and fulfill regulatory membership requirements.

1. **Composition of the IRBs:** The composition of each **IRB** shall be in compliance with [45 CFR 46.107](#) and [21 CFR 56.107](#), which require:

- at least five members with varying backgrounds and professional competence appropriate for the type of research reviewed by the IRB,
- at least one member whose primary concerns are scientific areas,
- at least one member whose primary concerns are non-scientific areas, and
- at least one member who is not otherwise affiliated with the institution, or a member of the immediate family member of an affiliated individual.

Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made on the basis of gender. No IRB may consist entirely of members of one profession [[21 CFR 56.107\(b\)](#)].

2. **Qualifications of chair:** The **IRB** chair should have, prior to appointment, a thorough working knowledge of federal regulations for the protection of human subjects, the Belmont Report, the terms of the UToledo Federalwide Assurance, IRB policies and procedures, as well as appropriate federal, state and local regulations and laws.
3. **Alternate IRB Members:** An IRB alternate member is a member of the IRB who may serve in the absence of a designated, primary member. Use of an alternate member results in two members for one IRB position. Only one member (either the primary or alternate) for each IRB position may participate in IRB business at one time. The IRB may not record a vote for both a primary and alternate member.

Alternate members' qualifications should be comparable to the corresponding primary member's qualifications to ensure that regulatory requirements for IRB composition are met. An alternate for a non-affiliated member should also be unaffiliated with UToledo. Alternates for scientific members should have expertise in the same or very similar area as the primary member. Alternates for non-scientific members should also be considered non-scientific.

4. **Appointment of Members:** The vice president for research will appoint members and alternates to serve on the IRB and shall name the chair of each IRB. Recommendations for appointments and re-appointments of individuals other than the chair may be made by the chair, vice-chair or another interested person.
5. **Term of Service:** Terms of members will be up to three years. There is no limit on the number of terms a member may serve. Members may be removed from the board through written notification from the vice president for research.
6. **Non-IRB Consultants:** In addition to regular members, the IRB may utilize outside experts as needed for adequate review of project. These may vary, except: (a) for FDA related drug studies, two persons licensed to prescribe the drugs must be included in the review process; and (b) when a project involves vulnerable subjects (e.g. prisoners,

**The University of Toledo Human Research Protection Program
Written Procedures**

children or mentally disabled) who will be at greater than minimal risk, a person will be included whose primary concern is the welfare of such subjects.

B. Responsibilities of IRB Members

1. **IRB Member Responsibilities.** IRB membership involves attending one regular meeting per month and reviewing study proposals prior to the meeting. Members may also be asked to attend an emergency meeting from time to time. IRB members should be prepared to devote several hours per month in preparation for and to attend the IRB meeting. Specific responsibilities of members include:
 - a) **Educational Training:** Complete the required IRB member education. Develop an understanding of the ethical principles and federal regulations for the protection of research participants. Participate in continued education through workshops, and reviewing current literature in the field, and education presented at IRB meetings.
 - b) **Review and Evaluate Proposed Research:** Contribute to the institution's human research protection program by participating in the review and evaluation of new research proposals and ongoing research investigations. Conduct a thorough review of study materials when appointed as a primary reviewer for a study and be prepared to summarize the study, critique the research and make a recommendation to the board regarding approval.
 - c) **Attend IRB Meetings:** Attend scheduled IRB meetings prepared to discuss proposals and items on the agenda within the member's realm of expertise.

VI. Application Requirements for IRB Review of Research

A. Submission Deadlines

Submission deadlines for review of convened research will be set by each IRB. Deadlines may be altered to accommodate holidays and departmental necessity. A schedule of submission deadlines and IRB meeting dates is available on the [HRPP web page](#), or by calling the HRPP.

B. Application Content for New Research

General Requirements: IRB applications that do not meet submission requirements, are incomplete or are improperly completed will be returned to the applicant. This could result in a delay in IRB review depending on the submission deadline. Items that must be submitted include, but are not limited to:

- A completed New IRB Research application
- A complete research protocol (Biomedical and Biomedical Cancer IRB submissions only);
- All appropriate informed consent forms, parental permission forms, assent forms, information sheets or justification for a request of waiver or alteration of the consent process, or a waiver of documentation of written consent, consistent with federal regulations 45 CFR [46.116 and 46.117](#) and for FDA-regulated research, 21 CFR [50 Subpart B](#);
- A literature search demonstrating justification for the proposed research;
- The most current version of the investigator's brochure(s) if applicable;
- All research data collection tools (surveys, questionnaires, etc.);
- All recruitment material or information to be given to subjects or potential subjects;

**The University of Toledo Human Research Protection Program
Written Procedures**

- **Human subject** training verification for any **study personnel** who have not previously submitted verification of training;
- Any additional information pertinent to the study that will assist the IRB in making the determinations set forth in these procedures;
- UToledo conflict of interest disclosure forms for **study personnel** (for unfunded and internally-funded studies, and for non-UToledo personnel on externally-funded studies);
- If research will be conducted at a non-UToledo site, letters on official letterhead or emails from an official business email address from the location, denoting what research activities are permitted to occur there;
- For FDA-regulated studies, IRB reviewers will also request as necessary any information or documentation such as a curriculum vitae (CV) or certifications for key personnel, or details about the proposed research site and equipment in order to ensure that the study team has the experience, qualified staff, and appropriate facilities to conduct the investigation;
- Any other document(s) listed on the IRB application

These requirements may be updated by the HRPP or IRB as necessary to conduct IRB business.

C. Application Requirements for Continuing Review

1. **Submission of Study Documents and Information for Continuing Review:** Principal investigators must submit all current study-related documents and report the progress of the study to the IRB through the Continuing Review Application.
 - a) **Required Documents:** The following items must be submitted to the IRB at the time the investigator applies for continued approval of a research study:
 - (1) A Continuing Review Application (see contents in section b, below);
 - (2) Data Safety Monitoring Board (DSMB) reports if applicable;
 - (3) Certain protocol departures that are to be reported only at the time of continuing review (see section VII.O.)
 - (4) UToledo conflict of interest disclosure forms for **study personnel** (for unfunded and internally-funded studies, and for non-UToledo personnel on externally-funded studies);
 - b) **Contents of Continuing Review Application:** Principal investigators must provide the following information and data to the **IRB**:
 - Verification of **study personnel** and any necessary updates on **human subject** training status
 - A summary of study purpose, procedures and progress
 - Any observed changes in risks / benefit ratio
 - Subject enrollment information, including the number of subjects enrolled locally and at other sites (if applicable)
 - Status of the subjects in the study, e.g. numbers of screen failures, currently active in study, in follow-up data collection only, completed intervention, withdrawals, and subjects lost to follow up
 - A summary of any instances of study non-compliance over the past approval period

**The University of Toledo Human Research Protection Program
Written Procedures**

- A summary of any serious adverse events
 - An explanation of any problems with obtaining or documenting informed consent
 - Any other information requested by the *IRB* on the continuing review application or through oral or written communication.
2. **Investigator Assurance:** At the time of continuing review, principal investigators must re-affirm their assurance of compliance and agreement to comply with investigator's responsibilities by signing where indicated on the Continuing Review Application.

VII. IRB Review of Research

A. Determination of Level of Review

1. **Assignment of Category:** *Human subject research* applications and protocols are pre-reviewed for completeness and preliminarily assigned to a level of review by HRPP staff. The HRPP staff may also determine that a certain application is not *human subject research* under the definitions set forth in [45 CFR 46.102](#). It is the prerogative of the IRB and HRPP staff to determine whether proposed research can be considered exempt under [45 CFR 46.104](#), and the IRB makes the final determination regarding which category of review (expedited or full board) is appropriate for the research.
2. **Exempt Determination:** Only IRB or HRPP staff may make exempt determinations; investigators may not make an independent determination that their research proposal is exempt. Exempt-designated *human subject research* that is conducted as proposed to the IRB is exempt from further *IRB* review.
3. **Discretionary Elevation of Level of Review:** Research that qualifies for exempt-level review may be reviewed by the *IRB* under expedited or convened review at the discretion of the *IRB* chair or vice chair. Research that qualifies for expedited review may be reviewed by the *IRB* under convened review at the discretion of the *IRB* chair or vice chair.

B. General Guidance Relevant to Initial and Continuing Review

In accordance with [45 CFR 46.108\(b\)](#), initial and continuing reviews of research must be conducted by the IRB at convened meetings with a quorum of members present, except where expedited review is appropriate under [45 CFR 46.110\(b\)\(1\)](#) or [21 CFR 56.110](#). Permissible categories of research that may be expedited are listed in the [Federal Register of November 9, 1998 \(63 FR 60364-60367\)](#), also listed in Appendix B of this document. The IRB must make the findings required by [45 CFR 46.111](#) or [21 CFR 56.111](#) (for FDA research) prior to approving *research*.

C. Expedited Review of Research

Research that is eligible for expedited review under federal guidelines may be reviewed under the expedited review procedures set forth in [45 CFR 46.110](#). At the discretion of the IRB chair or vice chair, research that is eligible for expedited review may be reviewed under the convened review procedures.

1. **IRB Members Authorized to Conduct Expedited Review of Research Proposals:** The IRB chair and any chair-designated IRB member from among experienced reviewers may conduct expedited review of research. A letter from the IRB chair designating an IRB member's authority to conduct expedited reviews shall be placed in the IRB member's file.

**The University of Toledo Human Research Protection Program
Written Procedures**

2. **Required Findings:** In addition to the findings required by [45 CFR 46.111](#), approval of research under the expedited review procedure requires that the reviewer find and document:
 - a) The research activities involve no more than minimal risk;
 - b) The research is within a permissible category justifying expedited review authorized by [45 CFR 46.110](#), or research for which limited IRB review is a condition of exemption under [45 CFR 46.104\(d\)\(2\)\(iii\)](#), [\(d\)\(3\)\(i\)\(C\)](#), and [\(d\)\(7\) and \(8\)](#). The reviewer shall document the specific category;
 - c) Identification of subjects and their response, or collected data, will not reasonably place them at risk of criminal or civil liability or be damaging to them (e.g. financial standing, insurability, reputation) unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal; and
 - d) The informed consent form is adequate, based on federal regulatory guidelines.
3. **Authority of Reviewer:** In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review by the convened IRB.
4. **Approval Period:** The approval of expedited research initially approved under the pre-2018 Federal Policy for the Protection of Human Research Subjects (“Common Rule”) requirements shall be valid for no more than one year from the date of review unless new information is obtained (e.g. serious unexpected events) and the chair determines that the study should be reviewed by the full board. Expedited research initially approved under 2018 Common Rule requirements (the “Final Rule” or “Revised Common Rule”) is not subject to an approval period unless appropriate justification for an approval period is provided by the reviewer. Expedited research without an approval period will require submission of Annual Progress Reports.
5. **Reporting Expedited Actions to the IRB:** Research proposals approved under the expedited review procedure shall be placed on the IRB agenda of the next IRB meeting. The agenda shall list the title of the study, the name of the principal investigator, and the IRB study number. The chair shall call these items to the attention of the board and allow time for any questions or discussion by the IRB. All study approval documents are available electronically for inspection by IRB members at any time.

D. Convened Review of Research

1. Process for Initial Convened Review of Research

- a) **Application Pre-Review and Processing:** New applications for convened review are submitted via the electronic submission system and pre-reviewed for completeness by HRPP staff. Studies are assigned an IRB number when assigned for review. The study is then listed on the agenda for the IRB meeting at which the study will be reviewed.
- b) **Primary Reviewer System:** Primary reviewer(s) are assigned to conduct an in-depth review of study documents. All other IRB members should review at a minimum a protocol summary (of sufficient detail to make the determinations required under [45 CFR 46.111](#) or [21 CFR 56.111](#)), the informed consent document, and any recruitment materials. The complete set of application

**The University of Toledo Human Research Protection Program
Written Procedures**

materials (described in Section VI.B above) is available electronically to all members for review.

2. IRB Voting and Actions:

a) **Definitions of Quorum and Majority**

- **Quorum:** Quorum refers to the minimum number and type of IRB members that must be present at a convened meeting in order to review proposed research. Quorum is met when a majority of the members of the IRB are present, including at least one nonscientist member. Members with a conflict of interest may not be counted toward quorum during review of the item for which they have a conflict of interest, however, the member's alternate may count toward quorum, and vote on the item in place of the member with a conflict of interest.
- **Majority:** A majority is calculated using the "half-plus-one" technique. For example, if the total IRB membership is 10, then the majority is 6. If the membership number is odd, the majority is calculated by taking half of the total number of members and rounding up to the next whole number, for example, a quorum for a 15-member IRB is 8.

b) **Review of Research at a Convened Meeting:** IRB review of research at a convened meeting shall be conducted in compliance with [45 CFR 46.108\(b\)](#) and [21 CFR 56.108\(c\)](#), which require that a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting. Members who miss a significant portion of IRB deliberations or do not understand the study or the issues should abstain from voting.

c) **Assurance of Minimized and Reasonable Risk:** Prior to approving any research project, the IRB must assure, regardless of category, that (a) risks to subjects are minimized, and (b) that risks are reasonable in relation to any anticipated benefits.

d) **IRB Actions:** Following IRB deliberations, the IRB chair shall call for a motion and second on the agenda item. For special items (for example, Deviation / Violation reports or Adverse Event reports), IRB members may make a motion to take any action appropriate to the item. For initial or continuing review of research protocols or for proposed amendments to approved protocols, members generally make a motion to take one of the actions below:

- **Approve as Submitted** – the item should be approved as presented to the IRB
- **Minor Modifications Required** - the board has concurred on explicit simple minor revisions, and the item may be approved after completion of those revisions, as verified by the chair or a designated IRB member
- **Major Modifications Required** - there are a substantial number of significant concerns, questions or problems with the item that cannot be addressed with minor modifications, so the item should be revised and returned to the full board for re-consideration

**The University of Toledo Human Research Protection Program
Written Procedures**

- **Defer** - the submission is incomplete and/or the IRB does not have enough information to adequately review the item
- e) **Voting:** After a motion has been made and seconded, the IRB chair shall call for a vote of the IRB members. Voting at a convened **IRB** meeting will occur only if a quorum of **IRB** members is present. Should the quorum fail during a meeting (e.g., by recusal of members with conflicting interests, early departures, or absence of a non-scientist member), the IRB may not vote unless a quorum can be restored. Voting may not occur if a member with a conflict-of-interest is present or if members have not had time to adequately discuss the research. A successful vote requires a majority vote of the quorum of members or their alternates (an alternate member may not vote if the regular member votes).
- f) **Voting Options:** A member has four options when voting:
- **Yes** (agree with motion)
 - **No** (disagree with motion)
 - **Abstain:** A member shall abstain from voting when the member feels that he or she should not vote on the item. Members who miss a significant portion of IRB deliberations or do not understand the study or the issues should abstain from voting. A member who abstains will be included for purposes of determining whether a quorum is present. Members who choose to abstain shall not have a conflict of interest.
 - **Recuse:** A member shall recuse himself or herself from voting when the member has a conflict of interest. A member with a conflict of interest may be in the meeting room for presentation of a research project but must leave the room during deliberation and voting. When a member recuses himself or herself, their alternate IRB member may be counted toward quorum and vote in their place; this substitution should be recorded in the meeting minutes, along with the name of the alternate member and the reason for recusal.
- g) **Review of Investigator's Response to Request for Minor Modifications**
- When the convened IRB approves a study with minor modifications, the IRB chair, the originally-assigned reviewer(s), or a chair-designated IRB member shall review an investigator's response to the IRB letter requesting specific minor clarifications or changes. If the investigator makes all requested clarifications or changes, the IRB chair or an assigned IRB member shall approve the research.
- If a satisfactory response is not received, the investigator shall be notified and may either revise their response or request re-review by the full board. If the investigator requests a re-review, the IRB will be notified at the next meeting that a satisfactory response was not received from the investigator. The investigator may be invited to the meeting to discuss the study with the board, provided the investigator leaves the meeting prior to any deliberations or voting by the board.
- h) **University Official Action:** UToledo officials may disapprove research that has been approved by the IRB, but they may not approve research that has not been approved by the IRB ([45 CFR 46.112](#)).

**The University of Toledo Human Research Protection Program
Written Procedures**

E. Continuing Review of Research

1. General Requirement for Continuing Review: Per federal regulations, all convened research studies and some expedited research studies are subject to continuing review at intervals determined by the IRB based on the risk to study subjects, not to exceed 12 months. Extensions of approval periods are prohibited.

- a) **Convened Review Research:** The appropriate length of approval is determined by the convened IRB using the procedures described in section E.3 below.
- b) **Expedited Review Research:** The approval period for expedited review research is generally one year for studies approved under pre-2018 Common Rule requirements, unless there are concerns regarding the primary investigator's experience, qualifications, or previous non-compliance. Expedited research approved under the 2018 Common Rule (Final Rule) requirements is eligible to forego continuing review unless the reviewer at the time of initial review requests continuing review for a specific and appropriate reason. All other expedited research approved under the Final Rule requires Annual Progress Reports to be submitted no less than annually to the HRPP.
- c) **Exempt Research:** Continuing review is not required for research classified as exempt; instead, an Annual Progress Report must be submitted no less than annually. Any change to a study's procedures that could elevate the review classification to expedited or convened must be reviewed by the IRB.
- d) **Annual Progress Reports:** For studies that do not require, or no longer require, continuing review by the IRB, Annual Progress Reports must be submitted electronically. This report requires the investigator to indicate that the study is still ongoing or to submit a Final Report to close out the study. For active studies, the report prompts the investigator to update personnel and conflict of interest information, to provide information about noncompliance and adverse events, and to attest that they will continue to meet PI responsibilities. Annual Progress Reports are reviewed by HRPP staff.

2. Continuing Review by the IRB:

- a) **Criteria for Continued Approval of Research:** The IRB uses the same criteria for approval during continuing review of research as is used for initial approval of research (see [45 CFR 46.111](#) and [21 CFR 56.111](#)).
- b) **Documents and Information Distributed to Members:** In conducting continuing review of research not eligible for expedited review, all IRB members will have electronic access to all study materials.
- c) **Review Process:** The IRB will follow the same process detailed in the explanation of the initial review of research, except that a report on the progress of the study and any changes related to the risk benefit ratio (as described above in Section VI.C) must also be reviewed.

Research reviewed under the expedited procedure during the last IRB review (initial or continuing) may undergo expedited continuing review if the research continues to qualify for expedited review. The primary reviewer or an individual authorized to make the determination that review of the research may be expedited must determine, that the research continues to qualify for expedited review.

**The University of Toledo Human Research Protection Program
Written Procedures**

3. **Determining Frequency of IRB Review:** The IRB member(s) / committee conducting the initial or continuing review (or otherwise as warranted) will determine continuing review at intervals appropriate to the research, but not less than once per year for convened research. Should the IRB member(s) / committee determine that expedited research requires continuing review, the reasons continuing review is required must be clearly documented. An approval period of no more than six months can be granted for Phase I *clinical trials* or research in which there is more than minimal risk involving a vulnerable population with no prospect of direct benefit to the individual participants. Examples of criteria used to make a determination on the frequency of review include, but are not limited to:
 - The nature of the study
 - The risks posed by the study and any minimization of those risks
 - The degree of uncertainty regarding the risks involved
 - The vulnerability of the subject population
 - The experience and qualifications of the research team
 - The projected rate of enrollment
 - Whether the study involves novel therapies
 - Any previous non-compliance or misconduct by the researcher(s)
 - The IRB's previous experience with the investigator and/or sponsor
 - Unanticipated problems, adverse events, and/or withdrawal of participants
 - For FDA regulated studies, the trial phase assigned by the FDA
 - Other criteria as determined by the IRB

4. **IRB Approval Period:** The calculation of the approval and expiration dates is as follows:
 - a) For initial review the date that the research is approved, or if modifications are required (to secure approval), the date that the modifications/conditions are met by the investigator (date of approval) is the "start date" for the approval period.
 - b) For continuing review the date that the research is re-approved, or if modifications are required (to secure approval), the date that the modifications/conditions are met by the investigator (date of approval) is the "start date" of the re-approval period.
 - c) The expiration date of convened research, and expedited research when applicable, is the last date of the approval period. Unless the IRB determines an earlier expiration date, the expiration date is one year (minus one day) from the date of approval.
 - For example, the expiration date for research that was approved on June 1, 2019, with a continuing review frequency of one year is May 31, 2020. Therefore, the last date that the research can be performed (unless the study is re-approved) is May 31, 2020.
 - d) Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review requires full review of the protocol.

5. **Documenting the approval period:** The approval period will be documented in the following locations by HRPP staff:
 - IRB meeting minutes
 - IRB study records

**The University of Toledo Human Research Protection Program
Written Procedures**

- IRB approval letter
6. **Communicating the IRB's Determinations Regarding the Approval Period to the Researcher(s):** Principal investigators are notified of the approval period in their IRB approval letter and, as a courtesy, may be reminded of upcoming expirations. It is the Principal Investigator's responsibility to be aware of and track approval and expiration dates and apply for continuing review in ample time for the IRB review process to be completed (two months prior to expiration is recommended).
 7. **Authority to Reduce Approval Period:** The IRB may reduce the time period of approval at any time during the approval period when warranted based on risk to subjects, investigator non-compliance or misconduct, or any other factor that could jeopardize the health or welfare of a study subject.

F. Verification of No Material Changes

The *IRB* will consider whether verification is required from sources other than the investigator that no material changes have occurred since previous IRB review, including the general criteria utilized to make the determination. Examples of when the IRB may require verification from other sources include but are not limited to:

- Pattern of Submitting Incorrect Versions of Required Documents
- History of Late Reporting of Adverse Events or unanticipated problems
- Previous Late Reporting of Changes in Research
- Report from a third party of deviation of approved research procedures
- Previous non-compliance or misconduct by the researcher(s)
- Continuing review report indicates changes not previously reported
- Randomly selected projects
- Complex projects

G. IRB Observation of Informed Consent Process

When deemed necessary by the IRB chair or the IRB members, the IRB will exercise its authority to observe or have a third party observe the informed consent process or the research ([45 CFR 46.109\(g\)](#)). This determination may be made during initial review, continuing review, following a report of an adverse or unanticipated event, following a report of investigator non-compliance, or at random as part of the IRB's compliance oversight responsibilities.

H. Emergency Review of Convened Research

1. **Emergency Meeting:** In exceptional circumstances, the IRB chair may call an emergency meeting of the *IRB* at his or her discretion to review a study or change to a research protocol. When requesting emergency review of research, the applicant should set forth in writing why an emergency meeting is justified. Standard submission requirements, other than submission deadlines, apply to emergency review of research. An emergency meeting will only be held if a quorum of the members is able to attend the emergency meeting.
2. **Procedure for Review:** Emergency review of research shall follow the same procedures as for the regular review of research, except that *IRB* procedures that are not a federal or state regulatory requirement may be altered to the extent necessary to complete review of the research under the circumstances.

I. Exempt Research

1. **Exemption Categories:** Research activities involving *human subjects* that meet federal exemption criteria are identified in [45 CFR 46.104](#). None of the exemptions apply to

**The University of Toledo Human Research Protection Program
Written Procedures**

research involving prisoners, fetuses, pregnant women, or human in vitro fertilization. Neither UToledo nor the IRBs may create a new category of exempt research.

2. Authority to Determine That Research Is Exempt:

- a) **Authorized Individuals:** A determination that research is exempt under [45 CFR 46.104](#) may be made by the following:
 - The **IRB** chair, vice chair or chair-designated reviewer
 - The HRPP staff
- b) **Unauthorized Individuals:** OHRP advises that investigators should not have the authority to make an independent determination that research involving **human subjects** is exempt. Therefore, investigators must check with the **IRB** or other designated authorities concerning the status of proposed research or changes in ongoing research prior to engaging in the research.

J. Reporting IRB Actions to Investigators

Investigators will receive written notice via the electronic application system of the action taken by the **IRB** in regard to their protocol.

1. **IRB Approval of Research:** Written notification from the **IRB** to the investigator gives the investigator IRB approval to conduct the proposed research as presented to the **IRB**. No involvement of **human subjects** (including tissues, data and other activities under the realm of **human subject research**) is permitted before such approval.
2. **IRB Request for Modifications Prior to Approval**
 - a) **Convened Review Research:** The specific modifications required by the **IRB** will be compiled by HRPP staff and the principal investigator will be notified of these required modifications via the electronic application system.
 - b) **Expedited Review Research:** The specific modifications required by the reviewer(s) will be compiled by HRPP staff and the principal investigator will be notified of these required modifications via the electronic application system.
3. **IRB Disapproval of a Research Study:** The HRPP staff will send written notification to the principal investigator when the convened **IRB** has disapproved the proposed study. The written notification will include the reasons for the disapproval, and information about how to respond to the **IRB** (45 CFR 46.109(d), 21 CFR 56.109(e)).

K. Reporting IRB Actions to University Officials

The HRPP staff member(s) supporting each **IRB** will send a finalized copy of monthly **IRB** meeting minutes, no less than quarterly to the vice president for research, who serves as the Institutional Official.

L. Student Research Projects

1. **Thesis and Dissertation Projects:** At the university level, a thesis or dissertation involving **human subjects** is not considered approved until the **IRB** has given approval relative to the use of those subjects. The appropriate faculty advisor or committee(s), as determined by departmental or college policies, should approve thesis and dissertation projects before submission to the **IRB** for review.
2. **Instructional Projects Using Human Subjects:** UToledo recognizes the need for diverse instructional projects utilizing human beings. However, UToledo makes no

**The University of Toledo Human Research Protection Program
Written Procedures**

exception to the principle that there is always an underlying responsibility for the protection of privacy, dignity, and welfare of human subjects in research. When comparing instructional projects and research projects, the difference lies not in the principles of sound and ethical practice, but in the focus of responsibility for monitoring compliance with those concerns.

- a) **Projects Not Considered Human Subject Research:** In a number of departments, it is customary for undergraduate courses to incorporate small projects that have many of the characteristics of research and involve using other persons as project resources. The usual purpose of these projects is to provide an opportunity for students to develop familiarity with the means of investigation customary to the various disciplines. These projects teach the development of student knowledge and skills. Collected data is not used for research purposes. To the extent that regular courses involve projects with this intention, which would not later be used as part of a research project, such projects do not meet the definition of *human subject research* and therefore do not need to be submitted to the **IRB** for approval. However, participation in such projects should be voluntary and based upon appropriate informed consent.
- b) **Projects That May be Considered Human Subject Research:** Internships, research practica, independent studies, independent research, honors projects, thesis, dissertation, and other formal research projects of undergraduate students, graduate students, faculty and staff. In addition, course projects that are classified by 45 CFR 46 and these Procedures as requiring IRB review must also be reviewed by the **IRB**.

M. IRB Determination of Significant Risk vs. Non-Significant Risk Devices

The FDA's investigational device exemption (IDE) regulations outline requirements for the approval and conduct of significant risk device studies and nonsignificant risk device studies ([21 CFR 812](#)), and describe certain types of device studies that are exempt from IDE regulations ([21 CFR 812.2](#)).

1. Definitions:

- a) **Significant Risk (SR) Device:** an investigational device that:
 - Is intended as an implant, and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - 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
 - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- b) **Nonsignificant Risk (NSR) Device:** an investigational device that does not meet the definition of a significant risk device.
- c) **Investigational Device Exemptions (IDEs):** the mechanism by which the FDA grants investigators special permission to conduct research using a new (not yet

**The University of Toledo Human Research Protection Program
Written Procedures**

FDA-approved) device or an FDA-approved device for a purpose or in a manner not already approved or cleared for use by the FDA. The FDA assigns an IDE number to a significant risk device and allows the investigation to begin after it determines that research participants will not be exposed to unreasonable risk.

2. Responsibilities for Making SR/NSR Determinations:

- a) **Sponsor** – The sponsor (or sponsor-investigator, if there is no separate sponsor as defined in [21 CFR 812.3](#)) is responsible for making the initial risk determination and presenting it, along with its rationale and supporting information, to the IRB. Sponsors may also request a risk determination directly from the FDA before applying for review of their proposed research study by an IRB.
- b) **IRB** – Unless the FDA has already made the SR/NSR determination, the IRB must make the SR/NSR determination at a convened meeting before the IRB can conduct its review of the study under [21 CFR 56](#). The IRB’s SR/NSR determination supersedes the decision of the sponsor.
- c) **FDA** – The FDA is available to assist the sponsors and/or IRBs in making these risk determinations. The FDA’s SR/NSR determination is final and supersedes the decisions of the IRB and sponsor.

3. IRB Procedure for Making SR/NSR Determinations:

- a) **Application Content** – The application is submitted by completing a New IRB Research application, as described in Section VI.B above. For device studies, the application collects descriptions of the device, the proposed investigational plan, subject selection criteria, the FDA status of the device, approved uses, and the proposed use of the device in the research study. Depending on whether the study is determined by the sponsor to involve a SR or NSR device, the application may also prompt for the sponsor’s rationale for the SR/NSR determination, or the IDE number and holder’s name if applicable. Additional elements that should be included in the application:
 - If applicable, FDA’s written determination of SR or NSR;
 - If applicable, reports from prior relevant investigations.
- b) **Criteria for Making the SR/NSR Decision** – in order to make this determination, the convened IRB will review the application materials described in section a) above. The IRB will consider the application materials in the context of the following issues in its decision:
 - The proposed use of the device; the risk determination is to be made based on the proposed use of the device in the investigation, not on the device alone;
 - The nature of the harm that may result from use of the device; SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject, as described in 1.a) above;
 - Any additional procedures that the subject will need to undergo as part of the investigational study; IRBs should consider potential harm associated with procedures as well as potential harm caused by the device.

**The University of Toledo Human Research Protection Program
Written Procedures**

When necessary, the IRB may obtain outside assistance, or request a determination from the FDA.

- c) **Documentation of the Decision** – the IRB’s determination and rationale for the determination will be documented in the meeting minutes. When applicable, additional documentation used to make the determination, such as the IDE approval letter or FDA’s written determination letter will be listed in the minutes and filed with the study application materials.

4. Study Review and Approval Procedure:

a) Nonsignificant Risk Device Studies

- If the IRB determines that the study is NSR, the IRB may review the study for approval based upon the criteria at [21 CFR 56.111](#).
- Upon IRB approval, the study may begin without submission of an IDE application to the FDA or any further approval from FDA. In the case of NSR studies, the IRB serves as the FDA’s surrogate for review, approval and continuing review of the NSR device study.
- NSR device studies must follow the abbreviated requirements for investigational device studies ([21 CFR 812.2\(b\)](#)); these abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports and prohibition against promotion of the device.
- For an NSR study to be eligible for expedited review, it must also present no more than minimal risk to the subject ([21 CFR 56.110](#))

b) Significant Risk Device Studies

- If the IRB determines that the study is SR, written notification will be provided to the clinical investigator and if appropriate, the sponsor, and retained with the application materials
- SR studies must have an IDE application approved by FDA before the study can begin. Sponsors may request IRB review of their SR device study before the IDE application is approved by FDA, however, the IRB will hold final approval of the study until the IDE application is approved. Once the approved IDE is uploaded via the IRB’s electronic application system, a reviewer may approve the application as described in Section VII.D.2.f of this document.
- SR studies must follow all of the IDE regulations at [21 CFR 812](#).

N. IRB Review of Humanitarian Use Devices (HUDs)

1. Definitions:

- a) **Humanitarian Use Device (HUD):** A HUD is defined as a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year ([21 CFR 814.3\(n\)](#)).
- b) **Humanitarian Device Exemption (HDE):** FDA may approve a HDE, which describes the indications for which the device is approved for marketing. The

**The University of Toledo Human Research Protection Program
Written Procedures**

approval is based on reasonable evidence that the device is safe under the conditions of use described in the labeling. A HDE is a humanitarian exemption from the “higher” standard of reasonable assurance of device effectiveness.

2. Requirement for IRB Review:

- a) **Use in Clinical Practice:** Non-investigational use of a HUD to treat or diagnose patients does not constitute research, but IRB review and approval are required prior to use on a patient at UToledo, unless the use of the HUD meets criteria for emergency use as described in [21 CFR 56.104\(c\)](#). An IRB can only grant approval for a clinician to use a HUD if the FDA-recognized sponsor has obtained a HDE.
- b) **Research:** Any proposed research collecting data on the safety or effectiveness of a HUD is also subject to IRB review and approval. Such studies must be conducted in compliance with the applicable IDE regulations ([21 CFR Part 50](#), [56](#), and [812](#)), unless the HUD is being studied for its HDE-approved indication.

3. Initial and Continuing Review Procedure for HUD Use:

- a) The request to use a HUD in medical practice shall be submitted using the “New IRB Research” application and must include information from the sponsor regarding the status of the HDE.
- b) Initial review of this application must occur at a convened IRB meeting following the process described in section VII.D of this document. The IRB will determine whether the proposed use of the HUD is clinical practice or research. HUDs may be approved by the IRB for use with groups of patients that meet certain criteria, under a protocol, or on a patient-by-patient basis.
- c) Use of a HUD requires informed consent; the standard UToledo Biomedical IRB informed consent template shall be used and amended as needed to remove references to participation in research. The patient must also be informed that the HUD is a device authorized under federal law for use; however, the effectiveness of the device for a specific indication has not been demonstrated.
- d) The clinician is responsible for obtaining continuing review approval from the IRB at least annually ([21 CFR 56.109\(f\)](#)).

4. **Reporting Requirements:** Adverse events and unanticipated problems that result from the use of a humanitarian device are subject to the same reporting requirements as for IRB-approved research, as described in section VII.O. of this document.

O. Reporting Research Issues to the IRB, University Officials and Federal Authorities

1. **Reportable Event:** The following events must be promptly reported to the **IRB** members, Institutional Officials, any relevant federal department or agency head, and **OHRP** when required by regulations:
 - a) Any unanticipated problems involving risks to subjects or others (hereinafter referred to as *unanticipated problems*);
 - b) Any serious or continuing noncompliance;
 - c) Any suspension or termination of IRB approval.

2. Definitions

**The University of Toledo Human Research Protection Program
Written Procedures**

- a) **Adverse Event** – per [OHRP guidance](#), an adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.
- b) **Internal Adverse Event** – those adverse events experienced by subjects enrolled by the institutional investigator
- c) **External Adverse Events** – those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the *clinical trial*.
- d) **Unanticipated Problem** – per [OHRP guidance](#), an unanticipated problem is any incident, experience or outcome that meets all three of the following criteria:
 - **Unexpected** (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
 - **Related or possibly related** to participation in the research (a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
 - **Serious**, which suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
- e) **Non-compliance** is defined as:
 - Failure (intentional or unintentional) to comply with applicable laws, regulations, institutional policies or HRPP written procedures governing research with human subjects; or
 - Any departure (deviation or violation) from an IRB-approved protocol
- f) **Deviation** - a departure from the protocol that has no potential substantive effect on the risks to participants or on the scientific integrity or the research plan or collected data.
 - Examples of a deviation include the accidental failure of investigators to perform a scheduled physical or blood test that was included in the approved protocol, or a subject’s failure to correctly self-administer a study drug.
- g) **Violation** - a departure from the approved protocol, without previous IRB-approval, that has the potential to cause harm or increase risk to participants, has the potential to affect the scientific integrity of the research, and/or impacts a subject’s safety, rights, or welfare.
 - Examples of a violation include failure to properly obtain informed consent, or using an unapproved consent form, enrollment of ineligible

**The University of Toledo Human Research Protection Program
Written Procedures**

subjects, or performing a research procedure not included in the approved protocol, or changing an approved study procedure such as using different dosing or infusion rates.

- h) **Serious Non-compliance** – is typically defined as an instance of non-compliance that meets any of the following criteria:
- Results in a substantive negative impact on the rights, welfare, privacy, confidentiality or safety of research subjects;
 - Significantly increases the risks and / or decreases the benefits associated with subject participation in the research;
 - Materially damages the scientific integrity of the research data;
 - Results in the conduct of non-exempt human subject research or significant modifications to research without IRB review and approval;
 - Results from willful or knowing misconduct on the part of the investigator.
- i) **Continuing Non-compliance** is typically defined as a situation that meets any of the following criteria:
- The investigator(s) has committed the same or similar instance of non-compliance repeatedly after having been notified of this type of noncompliance by the IRB;
 - The primary investigator has failed to respond within a reasonable timeframe to a request from the IRB to resolve an instance of noncompliance;
 - A pattern of frequent instances of documented noncompliance across one or more of an investigator's protocols that indicates a lack of understanding of human subject protection requirements or suggests the potential for future serious noncompliance in the absence of intervention.

3. Procedures and Operational Details for Investigator Reporting of Adverse Events and Unanticipated Problems to the IRB

- a) Items to report within 48 hours of discovery or notification:
- An internal death the investigator determines to be directly related / possibly related to a study intervention (not natural causes or underlying disease progression);
 - Events resulting in temporary or permanent interruption of study activities by the investigator, sponsor, or data safety monitoring board (DMSB) to avoid potential harm to subjects.
- b) Items to report within 10 working days of discovery or notification:
- Internal unanticipated problems;
 - Any internal incident, experience or outcomes that is related / possibly related, serious AND unexpected;

**The University of Toledo Human Research Protection Program
Written Procedures**

- Any internal adverse event that an investigator believes could influence the safe conduct of the research.
- c) Items to report at the time of continuing review:
- Internal adverse events that are related / possibly related but are not deemed to be anticipated problems (i.e., related / possibly related, unanticipated, not serious);
 - A summary of external adverse events that increased risk to subjects or others.
- d) Items that should not be reported:
- Internal adverse events that are unrelated to the study;
 - Internal adverse events that pose no more than minimal risk to subjects;
 - Individual external adverse events.
- e) The investigator will include the following information:
- A clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and
 - A description of any proposed protocol changes or other corrective actions taken by the investigators in response to the unanticipated problem.
4. **Procedures and Operational Details for Investigator Reporting of Noncompliance to the IRB**
- a) If the decision to depart from the approved protocol is under the control of the PI (for example, the PI decides to delay treatment due to lab results or other findings), the PI should inform the IRB as soon as possible by submitting a Single Subject Exception form to be reviewed and approved prior to departing from the protocol, unless the decision is made to avoid an increase in risk to the subject, such as a negative impact to the subject's rights, safety or welfare. In such a case, the deviation/violation should be reported to the IRB within 10 working days (5 working days for FDA-regulated device studies) after the departure occurs using the Protocol Deviation/Violation form.
- b) If the decision to depart from the approved protocol is not under the control of the PI (for example, if there is an unavoidable scheduling conflict, the subject fails to complete all necessary steps/tasks required of them, or a member of the research staff makes an error), the PI should submit a Protocol Deviation/Violation form to the IRB within 10 working days only in the event that the departure from the protocol will or could possibly adversely affect the subject's rights, safety or welfare or if the departure has or will impact the science of the study. If neither of these impacts will occur, the departure should be tracked and reported at the time of continuing review.
5. **Procedures and Operational Details for Reporting to University Officials and Federal Authorities**
- a) Upon receipt of information indicating a potentially reportable event, the HRPP and IRB shall promptly investigate the potentially reportable event.

**The University of Toledo Human Research Protection Program
Written Procedures**

- b) The IRB is responsible for making the determination as to whether serious or continuing noncompliance, or an unanticipated problem has occurred. The IRB also has the authority to suspend or terminate IRB approval for research. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action.
- c) If the IRB determines that a reportable event has occurred, the IRB chair shall inform the vice president for research, who serves as the Institutional Official.
- d) The vice president for research shall communicate any reportable events (including a statement of the reasons for the IRB's suspension or termination or approval if applicable) no later than seven (7) business days after the event is determined to be considered a reportable event to:
 - Other institutional official(s) as appropriate, such as the investigator's department chair, dean and/or the UToledo president.
 - If applicable OHRP (research covered by the UToledo Federalwide Assurance); and
 - If applicable, FDA or other federal agencies (research subject to FDA or other federal agency regulations)

P. IRB Review of Adverse Events and Unanticipated Problems

1. Responsibilities

- a) Federal regulations require prompt reporting of unanticipated problems involving risks to subjects or others to the IRB, institutional officials, and federal department or agency heads as appropriate ([45 CFR 46.108\(a\)\(4\)](#), [21 CFR 56.108](#)).
- b) Investigators are responsible for reporting certain adverse events and all potential unanticipated problems to the IRB, as described in Section VII.O of this document. Investigators, sponsors and sponsor-investigators of FDA-regulated research are also subject to additional reporting requirements ([21 CFR 312.32](#), [21 CFR 812.150](#)).
- c) The IRB is charged with reviewing and determining the appropriate course of action with respect to adverse events (UToledo policy [#3364-70-05](#)). The IRB will determine whether an event meets federal reporting criteria, and the IO will communicate reportable events to the appropriate officials as described in Section VII.O.
- d) Ensuring subject safety is a responsibility of both investigators and the IRB. Investigators may pause or terminate study activities to prevent harm to research subjects; this must be reported to the IRB promptly. The IRB has the authority to suspend or terminate approval of research that has been associated with unexpected serious harm to subjects ([45 CFR 46.113](#), [21 CFR 56.113](#))

2. **Contents of Reports to the IRB** – Reports of certain adverse events and all unanticipated problems are submitted via an Adverse Event Report form or may be summarized at the time of continuing review. The Adverse Event form, which is associated with an approved study, automatically imports information about the research protocol title, number, investigator name and contact information, sponsor name, and approval period. The following additional information is to be provided by the investigator:

**The University of Toledo Human Research Protection Program
Written Procedures**

- A detailed description of the event, incident, experience or outcome, including the date, subject ID number and location of the event
 - Information about whether a drug, device or procedure was involved, and whether the event has been reported to (if applicable) the sponsor and/or FDA
 - An evaluation of whether the event, incident, experience or outcome might be considered an unanticipated problem, by explaining whether it was serious, unexpected, and related or possibly related to the study procedures.
 - A description of any changes to the protocol or consent form, or corrective actions that have been taken or are proposed in response to the problem
 - An evaluation of whether the risks or benefits of the study require reassessment, whether the subject will remain enrolled, and whether the research project itself should continue.
3. **Initial Review of Adverse Events and Unanticipated Problems** – when reviewing reports of adverse events and unanticipated problems, the IRB should consider whether the affected research protocol still satisfies the requirements for IRB approval under the relevant federal regulations ([45 CFR 46.111](#), [21 CFR 56.111](#)). In particular, the IRB should consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits.
- a) **Adverse Event Report forms** will be pre-screened for completeness, and assigned to the relevant IRB chair, vice chair, or chair designee for review. The reviewer may request additional information from the PI, study staff, HRPP staff or others as necessary. All Adverse Event Reports will be acknowledged via a letter to the PI and all will be either reviewed or reported at a convened meeting. Potential outcomes of the initial review may include:
- No further actions required;
 - Revisions to the protocol or consent documents are required, with changes to be reviewed by the original reviewer;
 - Approval of the revisions proposed in the Adverse Event Report;
 - Requirement that subjects be notified of changes in the protocol or consent documents as a result of the adverse event or unanticipated problem;
 - Performing a retrospective review of adverse events reported for the research protocol (if the adverse event was reported by the investigator as being related to a research intervention, then an assessment of the adverse events across other research protocols involving the same experimental intervention will be performed);
 - Determination that the item may constitute an unanticipated problem (i.e., is related or possibly related to the study, unexpected, and serious, as defined in Section VII.O) and therefore should be reviewed by the convened IRB;
 - The IRB chair (or vice-chair, if the chair has a conflict of interest or is not available) has the authority to suspend some or all research activities if exceptional human subject safety issues are identified. This authority is

**The University of Toledo Human Research Protection Program
Written Procedures**

only exercised if an action is required prior to a convened meeting and it is not feasible to assemble an emergency meeting. When this authority is exercised, the PI will be notified by the chair or vice-chair immediately, and the decision will be reported at the next convened IRB meeting. The PI may voluntarily pause enrollment or research procedures to facilitate investigation; this should be communicated to the IRB, but is not considered a reportable event.

- b) **Items Reported at the Time of Continuing Review** will be reviewed by IRB members at the expedited or full board level as described in Section VII.E of this document. At the expedited level, the reviewer may require additional information, study or consent form modifications, and/or subject notification of changes in the protocol or consent form. The reviewer may elevate the item for full board review or action by the IRB chair (for example, if exceptional human subject safety issues are identified, or the item may meet criteria for an unanticipated problem).

4. Convened IRB Review

- a) **Materials to be Reviewed** - all relevant materials (for example, Adverse Event Reports, Continuing Review applications, summaries of relevant correspondence, the research protocol, consent forms) will be distributed to IRB members in advance of the meeting. In all cases, the IRB should be provided with a written summary of the adverse event, incident, experience or outcome, and any steps taken to protect other subjects or prevent recurrence.
- b) **Review Process** - a primary reviewer (usually the IRB chair) will be designated to lead discussion. The IRB should consider whether the research still meets criteria for IRB approval under federal regulations, and whether the risk / benefit ratio is altered or remains acceptable. The IRB will make a determination on the item by majority vote of a quorum of the members at the convened meeting. Individuals with a conflict of interest may not participate in the discussion or voting.
- c) **Potential Actions** - the convened IRB will review the relevant materials and make a determination of whether the adverse event, incident, experience or outcome constitutes an unanticipated problem, and whether any actions should be taken on the item. Actions that may be taken by the IRB may include but are not limited to:
- Requesting additional information from the investigator, sponsor, study coordinating center, or DMSB or data monitoring committee (DMC);
 - Determining that the item does not meet criteria as a reportable event;
 - Determining that the item does meet criteria as an unanticipated problem (i.e., is related or possibly related to the study, unexpected, and serious, as defined in Section VII.O);
 - Approval of study modifications proposed by the investigator as part of the item report;
 - Requiring or recommending modifications to the research procedures, study materials, or consent forms;
 - Requiring additional follow-up or monitoring of current or past research participants;

**The University of Toledo Human Research Protection Program
Written Procedures**

- Requiring increased reporting and / or a shortened approval period;
 - Elevating the study review level;
 - Requiring that additional information be provided to current or past research participants;
 - Requiring re-consenting of current research participants;
 - Suspension of IRB approval of the study, as described in Section XI.G of this document;
 - Termination of IRB approval of the study, as described in Section XI.G. of this document
- d) **Reporting of IRB Actions** – In all cases, the PI will receive written notification from HRPP staff of the decisions and actions of the IRB. If the IRB finds that an unanticipated problem has occurred or if the IRB decides to suspend or terminate IRB approval for the research, these events shall be promptly reported by the IRB chair to the vice president for research, who serves as the Institutional Official. The vice president for research will promptly communicate any of these reportable events to appropriate officials and/or agencies as described in Section VII.O.5 above.

VIII. IRB Operations and Record Keeping

A. Responsibility for Maintenance of Records

All records, files and materials of the *IRB* will be maintained through the *HRPP*, under the direction of the *HRPP's* associate director of research compliance.

B. IRB Records and Documentation

1. **Contents of IRB Research Files.** IRB research files shall contain the following:

- a) All information stipulated by federal regulations at [45 CFR 46.115\(a\)\(1\), \(3\), \(4\) \(7\) and \(8\)](#):
 - (1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, consent / assent / parental permission documents, progress reports submitted by investigators, and reports of injuries to subjects,
 - (2) Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in [45 CFR 46.109\(f\)\(1\)](#);
 - (3) Copies of all correspondence between the IRB and the investigators,
 - (4) Statements of significant new findings provided to subjects, as required by [45 CFR 46.116\(c\)\(5\)](#);
 - (5) The rationale for an expedited reviewer's determination under [45 CFR 46.110\(b\)\(1\)\(i\)](#) that research appearing on the expedited review list described in [45 CFR 46.110\(a\)](#) is more than minimal risk
- b) Completed IRB forms (e.g. applications, requests for amendments, adverse event reports, final reports);

**The University of Toledo Human Research Protection Program
Written Procedures**

- c) IRB approval memorandums; and
 - d) The following additional items, when applicable:
 - (1) Grant information
 - (2) *Clinical trial* agreement
 - (3) Conflict of interest forms
 - (4) Investigator brochure
 - (5) Sponsor generated amendment information
 - (6) UToledo IRB-approved Authorization for Use and Disclosure of Protected Health Information (PHI) forms (if not included in consent form)
 - (7) UToledo IRB-approved assent forms
 - (8) Med Watch forms (FDA safety information and adverse event reporting)
 - (9) Sponsor safety updates and sponsor adverse event information
 - (10) Data Safety Monitoring Board (DSMB) reports and updates
 - e) Information regarding research at non-UToledo sites, when applicable:
 - (1) Institutional or site permission letters from non-UToledo sites
 - (2) IRB Approval Memos and Approval Consent/Assent Authorization Forms from non-UToledo Sites
 - (3) Correspondence from non-UToledo sites
2. **Minutes of IRB Meetings.** Minutes of IRB meetings will be maintained in electronic format.
- a) **General Content of Minutes:** Minutes of IRB meetings shall be in conformance with [45 CFR 46.115](#), which requires
 - (1) sufficient detail to show attendance at meetings;
 - (2) actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining;
 - (3) the basis for requiring changes in or disapproving research, a written summary of the discussion of controverted issues and their resolution.
 - b) **Risk and Approval Period:** IRB minutes shall contain documentation regarding risk and approval period as described in these procedures.
 - c) **Other Content:** IRB minutes shall document specific findings required by federal regulations as described below (“IRB Documentation of Other Specific Findings”).
3. **IRB Documentation of Other Specific Findings:** When federal regulations require specific findings by the IRB, the IRB shall make and document such findings.
- a) **General Policy:** For research reviewed through the convened or expedited review process, when applicable, the IRB shall document its findings regarding alternative consent procedures; waiver of signed consent; research involving pregnant women, human fetuses, or neonates, research involving prisoners; and research involving children.

**The University of Toledo Human Research Protection Program
Written Procedures**

- (1) **Convened Review:** All required findings should be fully documented in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.
 - (2) **Expedited Review:** The IRB chair or chair-designated reviewer should document all required findings and file such documentation in the IRB study file.
- b) **Alternative Consent Procedures**
- (1) **General Requirement for Waiver or Alteration of Consent:** The IRB shall make and document the findings required by [45 CFR 46.116\(f\)\(3\)](#) when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent.
 - (2) **IRB Documentation:** When the convened IRB approves research that includes a waiver or alteration of the consent process, the federally-required findings should be documented in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.
- c) **Waiver of Obtaining a Signed Consent Form:** The IRB shall make and document the findings required by [45 CFR 46.117\(c\)](#) when approving a procedure which waives the requirement for obtaining a signed consent form.
 - d) **Research Involving Pregnant Women, Human Fetuses, or Neonates:** The IRB shall make and document the findings required by [45 CFR 46.204-207](#) when approving research involving pregnant women, human fetuses, or neonates.
 - e) **Research Involving Prisoners:** The IRB shall make and document the findings required by [45 CFR 46.305-306](#) when approving research involving prisoners.
 - f) **Research Involving Children:** The IRB shall make and document the findings required by [45 CFR 46.404-408](#) and [21 CFR 50 Subpart D](#) when approving research involving .
4. **Documentation of Risk and Approval Period.** The IRB must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [45 CFR 46.109\(e\) and \(f\)](#). IRB minutes must clearly reflect these determinations regarding risk and approval period.
 5. **Retention of IRB Records.** IRB records shall be retained for at least 3 years.

IX. Investigator Responsibilities

Investigators and research staff are responsible for familiarizing themselves with and complying with all UToledo policies and HRPP procedures, ethical standards for conducting human subject research and any applicable laws and regulations. Principal investigator responsibilities are listed in Section 6 of the UToledo policy ([#3364-70-05](#)) and are also communicated to investigators as part of written notification of study approval.

**The University of Toledo Human Research Protection Program
Written Procedures**

X. Research Conducted Off-Campus or With a Non-UToledo Researcher

Principal investigators planning to conduct *human subject research* at sites other than UToledo or with non-UToledo investigators must meet certain requirements of the *HRPP* and *IRB*. Requirements for conducting off-campus research range from a simple letter of permission from the site to a formal dual-review process.

A. Investigator Responsibilities

1. **Compliance with UToledo Federalwide Assurance:**
2. **Submit Written Description of Off-Campus Research to the IRB:** A principal investigator must submit a written description of the non-UToledo institution's involvement and of any non-UToledo investigator's or *study personnel's* participation to the HRPP prior to beginning any research activity. The description shall also include the following information:
 - a) All research sites, including (1) the address of non-UToledo sites, and (2) Whether the site holds a Federalwide Assurance
 - b) All research staff, including (1) institutional affiliations of each person, and (2) title and address of each person.
3. **Additional Prerequisites:** The *IRB* will notify the principal investigator of any additional requirements that must be met prior to beginning the research. The principal investigator is responsible for completing those requirements prior to beginning the research. Examples of prerequisites include, but are not limited to:
 - a) A letter of permission from a non-assured research site when all investigators are UToledo faculty, staff or students, or
 - b) Execution of an individual investigator agreement drafted by the HRPP for research conducted at a non-assured site in collaboration with an investigator who is not a UToledo faculty, staff or student member.

B. Collaborative Research with Researchers or Institutions That Are Not Federally Assured

1. **General Requirements**
 - a) The research is being conducted under the direction and supervision of a principal investigator from UToledo (the assured institution)
 - b) The collaborating institution or investigator does not hold a Federalwide Assurance (hereafter referred to as non-assured institutions) and does not routinely conduct human subjects research.
 - c) Extension of UToledo's Federalwide Assurance to cover collaborating individual investigators
2. **Types of Collaborations:** *UToledo-Related Research* may involve one of two types of collaborating individual investigators: collaborating independent investigator, or a collaborating institutional investigator.
 - a) A collaborating independent investigator is:
 - (1) not otherwise an employee or agent of UT;
 - (2) conducting collaborative research activities outside the facilities of UT; and
 - (3) not acting as an employee of any institution with respect to his or her involvement in the *UToledo-Related Research*.

**The University of Toledo Human Research Protection Program
Written Procedures**

- b) A collaborating institutional investigator is:
- (1) not otherwise an employee or agent of UToledo;
 - (2) conducting collaborative research activities outside of UToledo facilities;
 - (3) acting as an employee or agent of a non-assured institution with respect to his or her involvement in the research being conducted by UToledo (the assured institution); and
 - (4) employed by, or acting as an agent of, a non-assured institution that does not routinely conduct human subjects research.

C. Research Conducted in Collaboration with a Federally Assured Institution

Research conducted in collaboration with external federally assured institutions shall be documented through an **IRB** agreement approved by the **HRPP** and signed by the signatory official or official's designee. Collaborative research includes:

1. Reliance on an external IRB holding a Federalwide Assurance
2. An external institution relying on a UToledo IRB for review of a protocol

The UToledo principal investigator should contact the IRB to initiate the IRB agreement process.

D. Reliance on a Central or Independent Institutional Review Board

UToledo may rely on external IRBs, including central IRBs (also called "single IRB" or "IRB of record") or independent (commercial) IRBs to oversee the review and management of certain studies. For multi-institutional studies, use of a centralized IRB (or "single IRB") process is encouraged and, in some cases, required ([45 CFR 46.114\(b\)](#)). A written reliance agreement is used to document UToledo's reliance on the external IRB for oversight of the research, and to describe the responsibilities that each IRB will undertake to ensure compliance with institutional policies and federal regulations. A fully-executed agreement between UToledo and the external IRB is required before UToledo may rely on that IRB for review.

1. **Use of a Central or Independent IRB:** Research studies may be sent to a central or independent IRB upon approval by the IRB chair, vice chair or chair designee. UToledo or the investigator may determine that a particular study should be reviewed on site due to a local concern within the institution or community.
2. **Qualifications of the External IRB:** UToledo will ensure that the external IRB is qualified to review and approve the human subject research by requiring that the external IRB is registered with OHRP and can positively attest that they will meet HHS and/or FDA federal human subject protection requirements as appropriate to the research being reviewed.
3. **Reliance Agreement Content** – The reliance agreement will describe the responsibilities that each institution will undertake to ensure compliance with federal regulations and with each institution's own policies and procedures. The agreement will also specify how the external IRB will communicate to UToledo its findings and actions related to the research under review. Information about local context and policies will be communicated by UToledo to the external IRB when appropriate in order to ensure appropriate review and protection of human subjects.
4. **Agreement Approval** – The vice president for research, who serves as the IO, will sign the agreement on behalf of UToledo.

XI. IRB Compliance Activities

A. Compliance Responsibilities

1. The **HRPP** is responsible for supporting **IRB** compliance monitoring and corrective action and ensuring compliance with relevant laws, regulations, and ethical standards. In those instances where there are concerns regarding non-compliance with regulations, institutional policies or IRB procedures, the HRPP and the IRB will take the actions described in these procedures. These procedures apply to all research activities of faculty, staff, students and others involved in human subject research at UToledo.
2. The **IRB** is responsible for making the determination that serious or continuing non-compliance has occurred, and has the authority to suspend or terminate IRB approval for research that is not being conducted in accordance with the IRB's requirements ([45 CFR 46.113](#) and [21 CFR 56.113](#)).
3. The vice president for research (the IO) is responsible for reporting serious or continuing non-compliance and any suspensions or terminations of IRB approval to applicable department or agency heads, OHRP, and / or FDA, as described in Section VII.O.5 above.
4. Investigators are responsible for reporting non-compliance to the IRB, as described in Section VII.O.4 above and in UToledo policy ([#3364-70-05](#)).

B. Compliance Support Visits – Compliance Monitoring

1. The HRPP and IRB will select human research studies at random to review for regulatory and institutional compliance. For-cause compliance support visits may also be conducted at the request of the IRB, IRB chair, or the HRPP. These visits shall be conducted in a manner that offers compliance support to investigators. IRB members and / or HRPP staff will conduct the visit.
2. All **clinical trials** conducted at UToledo are subject to internal audit inspections (including targeted, for-cause, and investigator-requested inspections) by the Jacobson Center for Clinical and Translational Research (JCCTR), per UToledo policy [#3364-70-28](#).
3. When suspected non-compliance is found during a compliance support visit, the person in charge of the visit shall submit a report of non-compliance to the HRPP, and if required by other UToledo policies, to others.

C. Non-Compliance Reporting

Any person or entity may report suspected or confirmed non-compliance. Mechanisms for reporting include:

- a) Submission of a Deviation / Violation form by the PI or study staff to report non-compliance as described in Section VII.O.4.
- b) Reporting of deviations in aggregate as part of a Continuing Review application where appropriate, as described in Section VII.O.4.
- c) Written notice to the IRB or HRPP; this may be submitted anonymously.
- d) Electronic mail notification or phone call to the HRPP staff:
 - Biomedical or Biomedical Cancer IRBs: IRB.Biomed@utoledo.edu

**The University of Toledo Human Research Protection Program
Written Procedures**

- SBE IRB: IRB.SBE@utoledo.edu
 - HRPP contact information:
<https://www.utoledo.edu/research/rsp/irb/StaffIRB.html>
- e) Contacting the University Compliance & Privacy Office at 419.383.6933. The Compliance Office website also provides an option to report anonymously via a compliance and ethics online reporting tool: <https://www.mycomplianceportal.com/>

D. Initial Review of Reports of Compliance Issues:

All reports of non-compliance will be investigated. Individuals with a conflict of interest may not participate in the investigation. Potential cases of scientific misconduct will be reported to the University's Research Integrity Officer for investigation.

1. **Deviation / violation reports** will be pre-screened for completeness by HRPP staff, and assigned to the relevant IRB chair, vice chair, or chair designee for review. The reviewer may request additional information from the PI, study staff, legal counsel or HRPP staff or others as necessary. All deviation / violation reports will be acknowledged via a letter to the PI, and will be noted at a convened meeting. Potential outcomes of the initial review may include:
 - For minor (not serious or continuing) compliance issues, the reviewer may, in consultation with HRPP staff (and if appropriate, the PI) require corrective actions or study modifications if necessary.
 - The reviewer, in consultation with HRPP staff may request a compliance monitoring visit to assess the study (and if appropriate, other related studies) as described in section XI.C above.
 - The reviewer, in consultation with HRPP staff may recommend further investigation by a CORE process as described in section E below.
 - The reviewer may bring the report directly to the convened IRB for review and determination as to whether serious or continuing noncompliance has occurred.
 - The IRB chair (or vice-chair, if the chair has a conflict of interest or is not available) has the authority to suspend some or all research activities if exceptional human subject safety issues are identified. This authority is only exercised if an action is required prior to a convened meeting and it is not feasible to assemble an emergency meeting. When this authority is exercised, the PI will be notified by the chair or vice-chair immediately, and the decision will be reported at the next convened IRB meeting. The PI may voluntarily pause enrollment or research procedures to facilitate investigation; this should be communicated to the IRB, but is not considered to be a reportable event (Section XI.G below).
2. **Non-compliance reported at the time of continuing review** will be reviewed by IRB members at the expedited or full board level as described in Section VII.E of this document. At the expedited level, the reviewer may require corrective actions or study modifications, or may elevate the item for full board review or action by the IRB chair. The convened IRB may address the reported non-compliance as described below in section F below.
3. **All other reports of potential non-compliance** (audit reports, anonymous reports, etc.) will be reviewed by an HRPP staff member together with the relevant IRB chair, vice chair or chair designee. The reviewers may request additional information from other

**The University of Toledo Human Research Protection Program
Written Procedures**

individuals (e.g., the PI, study staff, legal counsel) as necessary. In all cases, the PI will receive written notification of the outcome. Potential outcomes of the initial review include:

- Dismissal of the allegation
- Requiring the investigator to submit a Deviation / Violation Report, with no further action required (for minor non-compliance issues)
- Recommendation or requirement of corrective actions or study modifications
- Initiation of a compliance monitoring visit to assess the study (and if appropriate, other related studies)
- Further investigation by a CORE process as described in section E below
- Bringing the report directly to the convened IRB for review and determination as to whether serious or continuing noncompliance has occurred
- The IRB chair and vice-chair have the authority to suspend some or all research activities if exceptional human subject safety issues are identified. This authority is only exercised if an action is required prior to a convened meeting and it is not feasible to assemble an emergency meeting. When this authority is exercised, the PI will be notified by the chair or vice-chair immediately, and the decision will be reported at the next convened IRB meeting. The PI may voluntarily pause enrollment or research procedures to facilitate investigation; this should be communicated to the IRB, but is not considered to be a reportable event (Section G below).

E. Compliance Oversight Review and Evaluation (CORE) Process

1. **Committee Formation.** The CORE Committee shall consist of at least three persons. The IRB chair or vice chair of the relevant IRB will serve as the chair of the CORE Committee. If neither of these individuals is available in a timely manner or if both have a conflict of interest, a designee(s) will be chosen by the IO. The CORE Committee chair will select the individuals to serve on the committee. Eligible individuals include:

- IRB members from any of the UToledo IRBs
- HRPP staff members (at least one HRPP staff member must be included as a member of the CORE committee)
- Other individuals as necessary to investigate the non-compliance

The CORE committee may request consultation or expertise from legal counsel or other individuals with relevant knowledge, insight or expertise.

2. **Committee Meeting with Investigator:** The HRPP shall send a written request to the researcher for a personal meeting with the CORE Committee. The written request shall provide a list of any initial documents or information requested by the committee, notify the researcher that he or she should provide any additional documents that would aid the committee in the investigation, and provide a deadline for submission of the documents. If the committee discovers during or after the meeting that additional documents are needed, the committee shall promptly request the documents from the researcher.

**The University of Toledo Human Research Protection Program
Written Procedures**

3. **Additional Meetings:** If deemed necessary, the HRPP shall make a written request for a meeting between any other person with relevant factual knowledge of the alleged non-compliance.
4. **Data Analysis and Preparation of CORE Committee Report:** The CORE Committee shall conduct an analysis of the information gathered and presented to the Committee and draft a report for review by IRB members. The report shall include the following elements:
 - A description of the allegations or indications of non-compliance;
 - Documentation of the results of pertinent investigations
 - A description of the responses (written and oral) from the investigators and any other individuals regarding the allegations or indications of non-compliance and any documentation submitted by or obtained from the researcher
 - A summary of IRB records (e.g., the IRB application, study approvals) that pertain to the allegation or indication of non-compliance
 - A suggested corrective action plan (if appropriate) for consideration by the IRB
5. **Report of Findings:** The CORE Committee shall submit the completed committee report to the relevant IRB for consideration.

F. Convened IRB Review of Alleged Non-Compliance

1. **IRB Responsibilities** – the convened IRB is responsible for making a final determination as to whether non-compliance has occurred, and whether it constitutes serious or continuing non-compliance.
2. **Review Procedure** – All relevant materials (for example, Deviation/Violation reports, CORE committee reports, summaries of relevant correspondence, the research protocol, consent forms) will be distributed to IRB members in advance of the meeting. In all cases, the IRB should be provided with a written summary of the noncompliance, the outcome of the noncompliance if known, and any steps taken to prevent recurrence. A primary reviewer (usually the IRB chair) will be designated to lead discussion. The IRB will make a determination on the potential non-compliance by majority vote of a quorum of the members the convened meeting. Individuals with a conflict of interest may not participate in the discussion or voting.
3. **Potential Actions.** The convened IRB will review the relevant materials and make an independent determination (by majority vote) of whether non-compliance has occurred, and if so, whether it meets criteria for serious or continuing non-compliance. The IRB will also determine by majority vote which sanctions or corrective actions, if any, should be instituted, based upon the nature of the noncompliance, the risk to participants, any steps already taken by the investigators to correct the problem or protect participants, and any previous non-compliance on the part of the study team. Actions that may be taken by the IRB may include but are not limited to:
 - a) Referring the report to an ad hoc committee for further study and reporting back to the convened IRB for re-review;
 - b) Dismissal of the complaint as unjustified;
 - c) Requiring or recommending modification of the research procedures or consent forms;

**The University of Toledo Human Research Protection Program
Written Procedures**

- d) Requiring that the PI and/or study team members undergo additional training or education;
- e) Requiring increased reporting and / or a shortened approval period for one or more of the investigator's IRB protocols;
- f) Requiring monitoring (including audits) of the research or consent process for one or more of the investigator's IRB protocols;
- g) Requiring that additional information be provided to current or past research participants;
- h) Requiring re-consenting of current research participants;
- i) Suspension of IRB approval for one or more of the investigator's studies, as described in Section XI.G below;
- j) Termination of IRB approval for one or more of the investigator's studies, as described in Section XI.G below;
- k) Recommending that the IO place temporary or permanent restrictions on human subject research practice, such as limiting privileges to minimal risk or supervised research projects;
- l) Designating all or part of the human subject research data as "not IRB approved"

4. Reporting of IRB Actions

- a) **To the Investigator** – in all cases, an IRB Notice of Action will communicate in writing to the investigator the IRB's decisions and a statement of the reasons for the IRB's action.
- b) **To Institutional Officials and OHRP:** If the IRB finds that serious or continuing non-compliance has occurred, or if the IRB decides to suspend or terminate IRB approval for the research, these events shall be promptly reported by the IRB chair to the vice president for research, who serves as the Institutional Official. The vice president for research will promptly communicate any of these reportable events to appropriate officials and/or agencies as described in Section VII.O.5 above.

5. **Institutional Review:** UToledo retains the right to review the findings and take additional corrective action, but may not prevent reporting to the OHRP or reverse any sanction on an individual investigator that has been imposed by the convened IRB.

6. Investigator's Right of Appeal

- a) **Purpose and Grounds for Appeal:** The purpose of an appeal is to give the investigator an opportunity to request reconsideration of the IRB's decisions under certain limited circumstances. Grounds for appeal are limited to those listed below; no other grounds will be considered:
 - new information not reasonably available during the investigation;
 - material failure to follow these policies and procedures;
 - the decision of the board is clearly erroneous; or
 - sanction exceeds the severity of the violations.

**The University of Toledo Human Research Protection Program
Written Procedures**

- b) **Process:** The investigator has the option to appeal the committee's decision if he/she disagrees with the findings and subsequent requirement(s). Appeals must be in writing, state the reason or reasons for appeal, and include any information that the investigator would like the appeals committee to consider. The written notice of appeal must be signed and dated by the investigator, and sent to the associate director of research compliance and the IRB chair. The appeal must be received within 14 days of the date of the IRB Notice of Action. Information that was reasonably available during the initial investigation and not submitted to the IRB in the initial investigation will not be considered on appeal. Decisions of the IRB will become final if a notice of appeal is not received within 14 days of the IRB Notice of Action.
- c) **Appeals Committee:** The Appeals Committee shall be comprised of three individuals appointed by the vice president for research. Appointees shall not have served on the CORE Committee for the initial investigation. The vice president for research may serve as a member of the Appeals Committee.
- The Appeals Committee will review the written statement of appeal by the researcher and make a recommendation as to whether the IRB should reconsider any aspect of its decisions based on the grounds outlined above. In reaching this recommendation, the Appeals Committee may seek a response from the IRB. The Appeals Committee shall complete its review within 60 days.

G. Suspension or Termination of Research

1. **IRB and University Authority:** The *IRB* has the authority to suspend or terminate approval of research that is not conducted in accordance with the regulatory, ethical, *IRB* and institutional requirements outlined in *IRB* policies and procedures or that has been associated with unexpected risk or harm to subjects (see [45 CFR 46.113](#) and [21 CFR 56.113](#)). Furthermore, any such unexpected risk or harm, suspension or termination will be reported to OHRP or the FDA if required by federal authority. University officials may also suspend or terminate approval of research under applicable UToledo policies.
2. **Circumstances in Which Suspending or Terminating IRB Approval Might Be Appropriate:** Reasons for suspending or terminating IRB approval include but are not limited to the occurrence of serious or continuing non-compliance, harm to research subjects, and unanticipated problems.
3. **Consideration of Subjects Already Enrolled** – When suspension or termination involves the withdrawal of current subjects, the IRB will consider the following:
 - Actions to protect the rights and welfare of currently enrolled subjects
 - Whether procedures for withdrawal of enrolled subjects take into account their rights and welfare (e.g. making arrangements for medical care, transferring to another investigator, continuation in the research under independent monitoring, etc.)
 - Informing current subjects of the suspension or termination
 - The need for any adverse events or outcomes to be reported to the IRB
4. **Ensuring Orderly Termination or Transfer of the Study** – In all cases where the IRB suspends or terminates approval for a study, the HRPP staff will communicate to

**The University of Toledo Human Research Protection Program
Written Procedures**

the investigator in writing the reason for the IRB's decision, the effective date of suspension or termination, and an explanation of any terms or requirements, such as notification or transfer of subjects, independent monitoring of the close-out process, or follow-up data to be reported to the IRB.

5. **Investigator-Initiated Suspensions and Terminations** – are not considered to be reportable events unless the IRB determines that serious or continuing non-compliance or unanticipated problems have occurred.
6. **Re-Instatement of Suspended IRB Approval** – Only the convened IRB may re-instate IRB approval. The decision to lift suspension of IRB approval may occur when the board members are satisfied that the concerns that led to the suspension have been appropriately addressed. Reinstatement of IRB approval will be reported by HRPP staff to the investigator and to vice president for research, who will communicate this information to all individuals or entities previously informed of the suspension, and others as necessary.

**The University of Toledo Human Research Protection Program
Written Procedures**

APPENDIX A: 45 CFR 46.111

45 CFR §46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(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 purposes.

(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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (i) The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.

(8) For purposes of conducting the limited IRB review required by §46.104(d)(7)), the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations: (i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the

**The University of Toledo Human Research Protection Program
Written Procedures**

requirements of §46.116(a)(1)-(4), (a)(6), and (d); (ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with §46.117; and (iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

APPENDIX B: Categories of Research That May Be Reviewed by the IRB through an Expedited Review Procedure

Source: 63 FR 60364-60367, November 9, 1998.

Applicability

- (A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be 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.
- (B) The categories in this list apply regardless of the age of subjects, except as noted.
- (C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- (D) The expedited review procedure may not be used for classified research involving human subjects.
- (E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
- (F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

- (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 increases the risks or decreases 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.
- (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 children², 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.

**The University of Toledo Human Research Protection Program
Written Procedures**

(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.

(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) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (Note: Some research in this category may be exempt from HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

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

(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 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.)

(8) Continuing review of research previously approved by the convened IRB as follows:

- (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
- (b) where no subjects have been enrolled and no additional risks have been identified; or
- (c) where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

**The University of Toledo Human Research Protection Program
Written Procedures**

1 An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

2 Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

The University of Toledo Human Research Protection Program
Written Procedures

APPENDIX C:

Findings the IRB Must Make and Document to Approve an Alternative
Consent Procedure

45 CFR 46.116

Please visit the “Regulations” web page at <http://www.hhs.gov/ohrp> for the most recent version of this regulation.

Code of Federal Regulations

TITLE 45 PUBLIC WELFARE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 46 PROTECTION OF HUMAN SUBJECTS

* * *

Revised October 1, 2019

* * *

46.116 (f). General waiver or alteration of consent

(1) Waiver. An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section, provided the IRB satisfies the requirements of paragraph (f)(3) of this section. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements at paragraph (d) of this section, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

(2) Alteration. An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (f)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.

(3) Requirements for waiver and alteration. In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

(i) The research involves no more than minimal risk to the subjects;

**The University of Toledo Human Research Protection Program
Written Procedures**

- (ii) The research could not practicably be carried out without the requested waiver or alteration;
- (iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- (iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.