

CWRU HRPP  
Investigator Manual

January 2025

*Table of Contents*

<b><u>CHAPTER 1 – PURPOSE AND SCOPE</u></b> .....	<b>9</b>
What Is the Purpose of This Manual? .....	9
What Is the Mission of CWRU’s Human Research Protection Program? .....	9
What Is the Function of the IRB at Case Western Reserve University? .....	10
Can the IRB Issue Retrospective Approval of Research That Has Already Been Conducted? .....	11
What Are the Consequences of Conducting Human Research Without Prior IRB Approval? .....	11
Who Should Submit to the Case Western Reserve University IRB? .....	11
Where Are Resources and Contact Information Located for the HRPP?.....	11
<b><u>CHAPTER 2 – OVERALL REGULATORY CLASSIFICATIONS AND DECISIONS MADE BY THE CWRU IRB</u></b> .....	<b>12</b>
What Is Human Research?.....	12
When Is IRB Approval Required? .....	12
<b>IRB ADMINISTRATION</b> .....	<b>13</b>
What are the different regulatory classifications that research activities may fall under? .....	14
What activities fall under Not Human Research? .....	14
What activities fall under the Exempt Category? .....	15
What Activities Fall Under the Exempt Review Category?.....	18
What Activities Fall Under the Expedited Review Category?.....	20
What Decisions Can the IRB Make in Review of Protocol Submissions? .....	23
Can The IRB Decision be Overturned? .....	24
Disagreeing With IRB Decisions .....	24
<b><u>CHAPTER 3 – HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) RESEARCH AND PRIVACY BOARD PROCESSES</u></b> .....	<b>25</b>
What is HIPAA?.....	25
Definitions Pertinent to HIPAA .....	25
What Is the Investigator’s Responsibility for HIPAA? .....	26
<b><u>CHAPTER 4 – RESEARCH WITH EXISTING SPECIMENS OR DATA</u></b> .....	<b>30</b>
Key Concepts to Consider Before Working With or Research Activities With Existing Specimens or Data.....	30
Definitions That Are Pertinent to Research With Existing Specimens or Data .....	30
Terms That Help the IRB Determine When IRB Approval is Required.....	30
What About Data or Samples from Decedents?.....	32
<b><u>CHAPTER 5 – REQUIRED TRAINING NECESSARY TO CONDUCT HUMAN SUBJECT RESEARCH</u></b> .....	<b>33</b>
Definitions Pertinent to Human Research Training .....	33
What Is the Continuing Research Education Credit (CREC) Program? .....	33
Who Is Required to Complete CREC Training? .....	33
What Happens If You Are Previously Certified at Other Institutions & Now Will Conduct Research at CWRU?.....	34
Can Investigators at Other Institutions Be Added to CWRU IRB Protocols? .....	34
What Are the Initial CWRU Certification Conditions? .....	34
What Are Opportunities to Earn CREC Credits to Renew a CREC Certificate?.....	35
What Is a CREC Credit Application? .....	36
When Is Good Clinical Practice (GCP) or Responsible Conduct of Research Training Required? .....	36
What Is the NIH Training Certification Letter Template? .....	36
<b><u>CHAPTER 6 – PRINCIPAL INVESTIGATOR AND STUDY TEAM MEMBER RESPONSIBILITIES</u></b> .....	<b>37</b>
Who Can Be the Principal Investigator of an IRB Protocol Submission? .....	37
What Are the Responsibilities of a Principal Investigator?.....	38
What Are Additional Basic Responsibilities of the PI During the Conduct of the Study? .....	44

Who Can Submit a New Protocol Submission to the IRB? .....	44
What Are the Responsibilities of the Study Team Members?.....	45
What Are the Requirements for Student-Driven Research?.....	45
What Are the Faculty Member Advisor Role & Responsibilities of Student-Driven Research?.....	46
Who Is Required to Complete a Conflict of Interests Disclosure Form?.....	46
What Are the Steps to Change the Principal Investigator on an Active IRB Protocol?.....	47
Principal Investigator CWRU Departure .....	47
What are PIs' responsibilities before leaving CWRU? .....	47
What are the 4 options the PI has to handle active IRB Protocols before leaving CWRU? .....	48
What happens if a PI goes on an unexpected Leave of Absence or departs from CWRU without transferring responsibility for their studies? .....	48
When Is a Study Administratively Discarded Due to Lack of Response? .....	49
For Protocols Reviewed by the Full Board.....	49

**CHAPTER 7 – IRB SUBMISSION COMPONENTS..... 50**

What Is the SpartaIRB System?.....	50
Who Should be Added to the Study Team Member Table on the SpartaIRB SmartForm?.....	50
What Are the Documents and Information Required for IRB Protocol Submissions?.....	50
What Information Should Be Included in the Protocol Template? .....	51
What Are the Detailed Requirements to Include in the IRB Protocol?.....	52
Regarding Protocols with Approval of IRBs from Other Institutions.....	59
Where Are the Informed Consent/Assent Forms Located?.....	59
What Are Study Modifications?.....	60
What Are the Requirements for a Modification Submission? .....	60
When Is a Continuing Review Required Under the Revised Common Rule (2018 Requirements)?.....	61
What Happens to Research Protocols That Are Initially or Previously Reviewed by a Convened Meeting? .....	62
What Happens to Research Protocols That Were Initially or Previously Reviewed by the Expedited Review Process?.....	63
What Happens to Protocols That Originally Underwent Full Board Review and Now Qualify for Expedited Continuing Review?.....	63
When Is a Continuing Review of a Protocol Required? .....	63
What Happens With Protocols That Were Approved Under the Pre-2018 Common Rule and Cannot Be Moved to the Revised Common Rule? .....	64
How Long Is a Protocol Required to go through the Continuing Review Cycle? .....	64
What Information Is Required to be Included in the Continuing Review Submission Sent to the IRB in the SpartaIRB System?.....	65
What Are the Principal Investigator's Responsibility to Prevent a Lapse in their Protocol?.....	66
What Steps Are Required to Close a Multi-Site Study When Each Institution Has Their Own IRB Approval?.....	66
What Steps Are Required to Close a Multi-Site Study That Involves a Single IRB Approval?.....	67
What Happens If a Protocol Submission Lapses?.....	67
What Are Circumstances When the IRB Would Allow Continuation of Study Interventions During a Lapse in Protocol? .....	68
What Is the Annual Check-In For Studies With No Expiration Date?.....	69
When Can an Approved IRB Protocol be Closed? .....	69
How Is a Study Closure Request Completed and Submitted to the IRB?.....	70
How Long Should Records be Retained? .....	70
Other IRB Submissions.....	71

**CHAPTER 8 – REQUIRED REVIEWS AND APPROVALS..... 72**

What Is a Department Scientific Review of Protocols?.....	72
What Are the Functions and Organization of a Department Scientific Review of Protocols?.....	72
What Are Additional Required Reviews? .....	73
CWRU Departments/Committees Utilized for Additional Reviews.....	73
CWRU Conflict of Interests (COI) Committee .....	74

Grants and Contracts Offices .....	74
Case Comprehensive Cancer Center Protocol Review and Monitoring Committee (PRMC).....	74
CWRU Human Stem Cell Research Oversight Committee (HSCRO).....	75
Office of Pre-Award Services and Agreements.....	75
CWRU Environmental Health and Safety Office .....	75
Radiation Safety Committee Review.....	75
School of Dental Medicine .....	76
<b><u>CHAPTER 9 – SPECIAL CONSIDERATIONS</u></b> .....	<b>78</b>
When Should a Suicide Risk Mitigation Plan Be Included in a Protocol Submission?.....	78
What Are Considerations for the Informed Consent Process of Studies that Include ONLY Questionnaires/Surveys?.....	78
What Is Required for Focus Groups or Interview Studies? .....	79
Audio Recordings .....	79
What Are Considerations for Blood Drawn for Research Purposes?.....	80
Adults.....	80
Children.....	80
Research Samples Requiring Additional Venipunctures.....	81
Multiple Samples .....	81
What Are Considerations for Studies Involving DNA and Genetics (Blood and/or Tissue)?.....	81
What Are Considerations for Studies That Include Chart Reviews? .....	81
Contact with Potential Participants from Chart Reviews.....	82
Can Chart Reviews Fall Under the Exempt Research Category? .....	82
Can An Investigator Access Their Own Patient Records for Research?.....	82
How Can An Investigator Gain Access to Another Investigator’s or Another Organization’s Records for Research? .....	83
Research Repositories.....	83
Pilot Studies .....	83
Clinical Trials.....	83
<b><u>CHAPTER 10 – GENERAL REQUIREMENTS FOR INFORMED CONSENT</u></b> .....	<b>85</b>
Definitions Pertinent to the Informed Consent Process .....	85
Principles of Informed Consent .....	86
What Guidelines Should PIs and Study Staff Follow to Ensure Comprehension During the Informed Consent Process?.....	86
What Are the General Requirements for Informed Consent Form of Non-Exempt Research? .....	86
What Are the Nine Basic Elements of Informed Consent?.....	87
What Additional Elements Must be Included When Appropriate?.....	88
What Are the Six Additional Elements of Informed Consent? .....	88
Additional Consent Form Requirements.....	89
What Is CWRU IRB’s Standard Research Consent Language? .....	89
What Are the CWRU IRB Consent Requirements?.....	91
What Are General Requirements of the Informed Consent Documents? .....	92
How Is the Health Insurance Portability and Accountability Act (HIPAA) Authorization to Use and Disclose Protected Health Information (PHI) for Research Purposes Used in the Informed Consent Document? .....	93
When Can a Waiver or Alteration of the Informed Consent Process Be Granted?.....	93
What is a Waiver of Signed Written Consent or Waiver of Written Documentation? .....	94
What Are the Requirements for Partial Waivers of Consent for Screening, Recruiting, or Determining Eligibility [§46.116(g)]?.....	95
What Are Requirements for Consenting and Debriefing for Deception Studies?.....	95
What Are the Requirements for Working with Schools in Research Projects?.....	95
What Is the Process to Comply with the Protection of Pupil Rights Amendment? .....	96
Electronic Informed Consent (eIC, e-Consent).....	97
What Happens When Children Reach Age of Majority During Their Participation in a Study?.....	98

What Are Additional Protections for Enrolling Decisionally Impaired/Cognitively Impaired Adult Participants in a Research Study? .....	98
What Is Documentation of Informed Consent [§46.117]? .....	99
What Are the Principal Investigator’s Responsibilities for Obtaining Consent? .....	99
<b><u>CHAPTER 11 – THE INFORMED CONSENT FORM</u></b> .....	<b>101</b>
What Is an Informed Consent Form? .....	101
Which Informed Consent Form Should My Study Use? .....	102
What is a Child Assent Form and when do I need to use one? .....	102
What Are Procedures to Enroll Non-English Speaking Participants? .....	103
What Is the Documentation of Consent Checklist? .....	104
How Can the Use of Fax, Mail, Online Sites, or E-mail be Applied to Document Informed Consent Process? .....	104
When Should A Participant Be Re-consented? .....	105
What Are Examples of When Re-consent is Required? .....	105
What Is a Certificate of Confidentiality (CoC)? .....	106
When Is a Certificate Issued and What Does it Protect? .....	106
What Are the Requirements for Posting of Clinical Trial Consent Forms [§46.116(h)]? .....	107
<b><u>CHAPTER 12 – REMUNERATION</u></b> .....	<b>108</b>
Definitions Pertinent to Remuneration .....	108
How Is an Appropriate Remuneration for Research Participants Determined? .....	108
What Should Be Considered for Remuneration in Research Involving Children? .....	109
What Are the Financial Reporting Requirements? .....	109
What Are CWRU Approved Methods to Compensate Research Participants? .....	109
<b><u>CHAPTER 13 – INVESTIGATIONAL DRUGS OR BIOLOGICS IN RESEARCH</u></b> .....	<b>110</b>
Ordering, Handling, Storage, and Disposition .....	111
<b><u>CHAPTER 14 – INVESTIGATIONAL DEVICES USED IN RESEARCH</u></b> .....	<b>114</b>
Definitions Pertinent to Investigational Devices .....	114
Investigational Device Exemptions (IDE) Regulations .....	115
Significant and Non-Significant Risk .....	117
Clinical and Translational Science Collaboration (CTSC) .....	117
Ordering, Handling, Storage, and Disposition .....	118
<b><u>CHAPTER 15 – INCLUDING CHILDREN IN RESEARCH</u></b> .....	<b>120</b>
Definitions Pertinent to Children Participating in Research .....	120
What Are Special Considerations When Enrolling Children in Research Studies? .....	121
What Is the Definition of a Guardian? .....	121
What Are Age Guidelines for Assent? .....	122
How to Obtain Verbal Assent .....	123
How to Request a Waiver of Assent .....	124
When Is an Alteration or Waiver of Parental Permission Permitted? .....	124
What Are Special Circumstances That Alter Standard Consent or Assent Criteria? .....	125
What Are the Office for Human Research Protections (OHRP) Criteria for Approval of Research That Involves Children? .....	126
<b><u>CHAPTER 16 – PREGNANT WOMEN AND NEONATES</u></b> .....	<b>128</b>
Definitions Pertinent to Recruiting Pregnant Women as Research Participants .....	128
What Are Special Considerations When Recruiting Pregnant Women and Fetuses? .....	128
What Are the Required Protections When Recruiting Pregnant Women and Fetuses? .....	128
What Are Additional Considerations When Recruiting a Pregnant Participant Who is a Child? .....	129

<b><u>CHAPTER 17 – PRISONERS AS RESEARCH PARTICIPANTS</u></b> .....	<b>130</b>
Definitions Pertinent to Involving Prisoners as Research Participants.....	130
What Are Ethical Considerations When Recruiting Research Participants Who Are Prisoners?.....	130
<b><u>CHAPTER 18 – DECISIONALLY IMPAIRED PERSONS</u></b> .....	<b>138</b>
Definitions Pertinent to Recruitment of Decisionally Impaired Persons.....	138
What Are Special Considerations When Recruiting People Who Are Decisionally Impaired?.....	139
What Are Important Protections to Include When Recruiting People who are Decisionally Impaired?.....	140
What Considerations Should Be Taken for Legal Authorized Representatives (LAR) and Research Consent?.....	142
What Should Be Taken Into Consideration for “Next-of-Kin” (NOK) and Research Consent?.....	142
What Are Approaches to Include Participants Who Possibly Have Impaired Decision-Making Capacity?.....	143
<b><u>CHAPTER 19 – OTHER VULNERABLE POPULATIONS</u></b> .....	<b>145</b>
What Additional Protections Should Be Included for Non-English Speaking Participants?.....	145
What Additional Protections Are Required When Recruiting University Students, Employees and/or Other Existing Relationships with Potential Research Participants?.....	146
What Are Other Classifications of Participants That Need Additional Protection?.....	147
What Is Community Based Participatory Research?.....	148
<b><u>CHAPTER 20 – RECRUITMENT</u></b> .....	<b>149</b>
How to Ensure There Is an Equitable Selection of Participants.....	149
How to Contact Potential Participants.....	149
How to Create Advertisements.....	150
What Are Restrictions for Payment for Recruitment?.....	151
<b><u>CHAPTER 21 – ETHICS CONSULTATIONS</u></b> .....	<b>153</b>
When Are Ethics Consultations Available or Required?.....	153
<b><u>CHAPTER 22 – INTENATIONAL RESEARCH</u></b> .....	<b>154</b>
When Is a Study Considered International Research?.....	154
What Are Additional Requirements to Conduct International Research?.....	154
What Are Special Considerations for Consent in International Research?.....	156
Does HIPAA Authorization/Privacy Rule Apply for International Research?.....	156
How Are Conflicts of Interest Considered for International Research?.....	157
<b><u>CHAPTER 23 – RESOURCES AND FACILITIES</u></b> .....	<b>158</b>
Clinical & Translational Science Collaborative (CTSC) FDA & Regulatory Support Core Under the UH FDA & Monitoring Support Core.....	158
<b><u>CHAPTER 24 – NON-COMPLIANCE INVOLVING HUMAN RESEARCH</u></b> .....	<b>159</b>
Definitions Pertinent to Non-Compliance.....	159
What Are The IRB Oversight Responsibilities to Evaluate Allegations of Non-Compliance?.....	160
How Does The CWRU IRB Review Non-Compliance Reports?.....	162
<b><u>CHAPTER 25 – QUALITY IMPROVEMENT PROGRAM (QIP) REVIEWS</u></b> .....	<b>165</b>
Overview of the Quality Improvement Program.....	165
What Is a Quality Improvement Program (QIP) Review?.....	165
<b><u>CHAPTER 26 – OVERVIEW OF CLINICALTRIALS.GOV RECORDS</u></b> .....	<b>167</b>
What Is ClinicalTrials.gov?.....	167
What Is a Clinical Trial?.....	167
What Are the FDA Requirements for ClinicalTrials.gov?.....	167



What Are NIH and Federal Funding Requirements for ClinicalTrials.gov?.....	168
What Is The International Committee of Medical Journal Editors and What Are Their ClinicalTrials.gov Requirements? ...	168
Which Office Can Help With ClinicalTrials.gov Records? .....	169
How to Register a New Study.....	170
What Are the Requirements for CT.gov Record Maintenance? .....	170
What Are Results Reporting Requirements?.....	170
<b><u>CHAPTER 27 – REPORTABLE NEW INFORMATION</u></b> .....	<b>172</b>
Definitions Pertinent to Reportable New Information (RNI).....	172
What Are Reporting Requirements for Investigators?.....	173
Protocol Deviations.....	176
Unanticipated Problems .....	177
Adverse Events .....	178
<b><u>CHAPTER 28 – RELIANT REVIEW AGREEMENTS FOR SINGLE IRB REVIEW</u></b> .....	<b>182</b>
What Are the Bases for Single IRB Review?.....	182
What Considerations and Requirements Does CWRU Impose for Reliant Reviews?.....	183
What Are the Steps for the Reliance Request and Acceptance? .....	184
What Is Required to Ensure the CWRU Site Consent Form Meets the Overall Study and Local Site Requirements?.....	185
What Are the Site PI’s Responsibilities for Reporting New Information and Submitting Modifications When Relying on an External IRB as the IRB of Record?.....	186
What Steps Are Required for the CWRU IRB to Consider Being the IRB of Record for Multi-Site Research?.....	186
What Are Different Types of Reliance Arrangements With Central and Commercial IRBs?.....	187
What Are Reliance Review Platforms?.....	187
What Are IRB Authorization Agreements (IAA)? .....	188
<b><u>CHAPTER 29 – REQUIREMENTS FOR A PRIME AWARDEE OF FEDERALLY FUNDED HUMAN RESEARCH</u></b> .....	<b>189</b>
What Are Requirements for a Prime Awardee of Human Research That Is Federally Funded?.....	189
<b><u>CHAPTER 30 – REQUIREMENTS FOR SMALL BUSINESS INNOVATION RESEARCH (SBIR)/SMALL BUSINESS TECHNOLOGY TRANSFER (STTR) GRANT RECIPIENTS</u></b> .....	<b>190</b>
Institutional (Small Business) Engagement in Human Research.....	190
Obtaining A Federal Wide Assurance (FWA) .....	190
Pre-Grant Submission Information .....	191
IRB Protocol Submissions .....	191
<b><u>CHAPTER 31 – ADDITIONAL REQUIREMENTS FOR DHHS-REGULATED RESEARCH</u></b> .....	<b>193</b>
<b><u>CHAPTER 32 – ADDITIONAL REQUIREMENTS FOR FDA-REGULATED RESEARCH</u></b> .....	<b>194</b>
<b><u>CHAPTER 33 – ADDITIONAL REQUIREMENTS FOR CLINICAL TRIALS (ICH-GCP)</u></b> .....	<b>199</b>
<b><u>CHAPTER 34 – DEPARTMENT OF DEFENSE RESEARCH</u></b> .....	<b>206</b>
<b><u>CHAPTER 35 – DEPARTMENT OF JUSTICE RESEARCH</u></b> .....	<b>207</b>
Additional Requirements for DOJ Research Conducted in the Federal Bureau of Prisons .....	207
Additional Requirements for DOJ Research Funded by the National Institute of Justice .....	209
<b><u>CHAPTER 36 – DEPARTMENT OF EDUCATION RESEARCH</u></b> .....	<b>210</b>
<b><u>CHAPTER 37 – GDPR REQUIREMENTS</u></b> .....	<b>211</b>

<b><u>CHAPTER 38 – PREPAREDNESS CONSIDERATIONS FOR AN EMERGENCY OR DISASTER</u></b> .....	<b>212</b>
Consider Different Types of Emergencies/Disasters.....	212
Deciding Whether a Study-Specific Risk Mitigation Plan for Ongoing Research Is Needed.....	212
Tools and Resources for Developing Study-Specific Emergency/Disaster Risk Mitigation Plans for Ongoing Research .....	212
Voluntary Holds on Human Research Activities.....	213
Submitting Study-Specific Emergency/Disaster Risk Mitigation Plans for IRB Review.....	213
Other Reportable New Information Considerations During Emergency/Disaster Scenarios .....	213
<b><u>APPENDIX A – CERTIFICATE OF CONFIDENTIALITY</u></b> .....	<b>214</b>
When Is a Certificate Issued, and What Does It Protect? .....	214
NIH Funded Studies.....	214
Non-NIH Funded Studies.....	215
IRB Requirements Relating to Certificates of Confidentiality .....	215
<b><u>APPENDIX B – ENSURING COMPREHENSION DURING THE INFORMED CONSENT PROCESS</u></b> .....	<b>216</b>
Overview .....	216
Suggested Open-Ended Questions .....	217
Employ Consent Quizzes for Online Studies.....	218
Determine Eligibility .....	218
When Including Children in Research.....	218
Resources .....	218
<b><u>APPENDIX C – CWRU RESEARCH PARTICIPANT PAYMENT GUIDANCE</u></b> .....	<b>219</b>
List of Payment Methods .....	219
IRS Information .....	219
<b><u>APPENDIX D – GUIDANCE FOR THE TRANSFER OF WHOLE GENOME SEQUENCING DATA TO CWRU</u></b> .....	<b>221</b>
Definitions Pertinent to Whole Genome Sequencing Data.....	221
Overview.....	221
Guidance .....	222



## CHAPTER 1 – Purpose and Scope

### What Is the Purpose of This Manual?

This “INVESTIGATOR MANUAL” (HRP-103) is designed to guide faculty, staff and students through processes, procedures, and resources related to the conduct of Human Research that are specific to Case Western Reserve University (CWRU). Additionally, the manual serves as a guide for the CWRU research community when preparing and submitting materials to the CWRU IRB. **Investigators and study staff are required to abide by the procedures as described in this manual.**

Along with this manual, current Human Research-related policies, SOPs, Worksheets, Checklists and templates may be found in the SpartaIRB online electronic protocol submission system. Collectively, the documents in the SpartaIRB Library create a complete picture of Human Research Protection Program (HRPP) and Institutional Review Board (IRB) expectations and a guide to seeking IRB review and approval. The documents in the SpartaIRB Library are also used by HRPP staff and IRB members to enhance compliance with federal, state and local requirements for conducting research and protecting human participants.

General information regarding human subject research protections and relevant federal regulations and guidance is incorporated into the required human protections training.

- For additional information see Chapter 2- Required Training.
- This manual and supporting documents, including the definitions and descriptions in “SOP: Definitions (HRP-001)” are helpful in the conduct of research.
- To ensure you are always referencing the most current version of the documents in the SpartaIRB Library, please access them in real time from the IRB website rather than downloading and storing them on your computer.
- We encourage you to use all of these resources to aid in the successful submission and conduct of your research.

### What Is the Mission of CWRU’s Human Research Protection Program?

The [HUMAN RESEARCH PROTECTION PROGRAM PLAN \(HRP-101\)](#) describes the University’s overall plan to protect participants in Human Research. It includes:

- The mission of the Human Research Protection Program.
- The ethical principles that the University follows governing the conduct of Human Research.
- The applicable laws that govern Human Research.
- When the University becomes “engaged in Human Research” and when someone is acting as an agent of the University conducting Human Research.
- The types of Human Research that may not be conducted.
- The roles and responsibilities of individuals within the University.

Visit the [Human Research Protection Program website](#) to learn more about the HRPP.

The mission of CWRU’s Human Research Protection Program (HRPP) is to protect the rights, dignity, welfare, and privacy of human research participants by ensuring that the oversight of human research is



appropriate and in accordance with institutional, federal, state and local requirements, as well as the ethical principles promulgated by the Belmont Report.

CWRU assures that all of its research involving human participants will comply with the Terms of Assurance for Protection of Human Subjects for Institutions within the United States (<http://www.hhs.gov/ohrp/assurances/index.html>).

- Research conducted outside of the jurisdiction in which CWRU resides is also subject to the same ethical and regulatory requirements, in addition to country/region specific requirements.
- This fundamental commitment to the protection of human participants applies to all CWRU research involving human participants, regardless of the funding source and regardless of the location of the research.

## What Is the Function of the IRB at Case Western Reserve University?

The Institutional Review Board (IRB) is an independent committee established by the CWRU Board of Trustees and the University's President. The CWRU IRB has been designated by the Institutional Official, who is the Senior Vice President for Research, to be the IRB relied upon by the HRPP.

The CWRU HRPP has under its jurisdiction one IRB committee that is responsible for reviewing research involving human participants conducted by CWRU faculty, staff and students. The CWRU IRB is a comprehensive IRB and reviews social, behavioral, educational, and low-risk biomedical Human Research studies.

The IRB is constituted appropriately according to the Federal Regulations to review research with the sole purpose of protecting the rights and welfare of human participants recruited to participate in research activities conducted under the auspices of the institution.

Some CWRU faculty members also have an appointment at one of CWRU's hospital affiliates.

- If the faculty member is conducting research that will involve hospital patients, their data, and/or a hospital facility or equipment, the affiliated hospital IRB will be the IRB of record.
- If the CWRU faculty member is conducting research under their role as a CWRU faculty member and not recruiting hospital patients or using their data, then the CWRU IRB can be the IRB of record.

The CWRU IRB will not provide or publish the names of the members of the IRB except to federal regulatory agencies requiring specific disclosure. Others, such as industry sponsors, may request a list of IRB members identified by initials and area of specialization.

The criteria for IRB approval include:

- Procedures for minimizing risk
- Favorable risk-benefit analysis
- Equitable subject selection
- Informed consent and parental permission
- Data monitoring
- Privacy and confidentiality
- Additional protection for vulnerable participants
- Test article accountability
- Scientific merit and feasibility

- Resources

## Can the IRB Issue Retrospective Approval of Research That Has Already Been Conducted?

No, the IRB will not review determination forms or research protocols if the research has already been conducted. When applicable, IRB review provides guidance to the investigator and assurance to the public that ethical considerations and risks related to the research have been considered, mitigated when possible, and determined to be appropriate.

## What Are the Consequences of Conducting Human Research Without Prior IRB Approval?

The consequences of conducting human participants research without prior IRB approval are significant and could include some or all of the following:

- Required destruction of any data collected without IRB approval
- Journals may not publish, or you may be prohibited from presenting, research findings
- Retraction of any published research findings
- Loss or clawback of funding
- Other academic disciplinary actions initiated by your department, college or the University strongly encourages seeking a determination

If you are concerned that research you conducted may have required IRB review, please email the IRB at [cwru-irb@case.edu](mailto:cwru-irb@case.edu).

## Who Should Submit to the Case Western Reserve University IRB?

CWRU faculty members, staff and students from any school or administrative unit within the University may submit a research protocol to the CWRU IRB. With rare exceptions, any study submitted to the CWRU IRB should have a CWRU faculty member as the Principal Investigator listed in the SpartaIRB system.

## Where Are Resources and Contact Information Located for the HRPP?

This document, the Human Research Protection Program plan and other resources are available on the HRPP Website. If you have any questions or concerns about the HRPP, contact the HRPP Administration Office at 216-368-0134, by email at [cwru-irb@case.edu](mailto:cwru-irb@case.edu), or in writing to:

Kim Volarcik  
Executive Director, HRPP  
Office of Research Administration  
10900 Euclid Avenue  
Cleveland, OH 44106-7230

If you have questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Research Protection Program that cannot be addressed by contacting the HRPP Administration Office, you may contact the Senior Vice President for Research or the Associate Vice President for Research.

## CHAPTER 2 – Overall Regulatory Classifications and Decisions Made by the CWRU IRB

### What Is Human Research?

The [HUMAN RESEARCH PROTECTION PROGRAM PLAN \(HRP-101\)](#) defines the activities that the University considers to be Human Research. An algorithm for determining whether an activity is Human Research can be found in the [WORKSHEET: Human Research \(HRP-310\)](#), located in the SpartaIRB Library.

- Use this document for guidance as to whether an activity meets either:
  - Department of Health and Human Services (DHHS) -OR-
  - Food and Drug Association (FDA) definition of Human Research
- Keep in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research for IRB oversight.

With respect to Human Research activities at the University:

1. You are responsible for following all IRB requirements for Human Research;
2. You may not conduct Human Research without prior IRB review and approval. The IRB will not review or approve research activity that has already occurred.
3. If you have questions about whether an activity is Human Research, see [Human Research Determination Form \(HRP-503\)](#).
4. See [WORKSHEET: Exemption Determination \(HRP-312\)](#) for activities that are exempt from IRB oversight.  
***Please note:*** You are required to still submit the study to the IRB for review and an exempt determination.
5. Human Research may be reviewed and approved by an external IRB in certain situations.

The CWRU IRB has the sole authority to determine whether an activity meets the definition of Human Research. When activities are conducted that might represent Human Research, the activities must be submitted to the IRB for a determination. An Investigator may request a determination that an activity is Not Human Research, but the final determination will be made by the IRB.

### When Is IRB Approval Required?

The responsibility for initial determination whether an activity constitutes research involving human participants rests with the CWRU IRB. If an investigator is not sure their research falls under the federal definitions of “human subject” and “research” ([45 CFR 46.102](#)), they may request a confirmation that an activity does not constitute human subjects research from the IRB Office. All requests must include sufficient documentation of the activity to support the determination.

Determinations regarding activities that are either clearly or clearly not human subjects research, may be made by the Research Compliance Officer or IRB administrators. Determinations regarding less clear-cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB. Documentation of all determinations made through the IRB Office will be recorded and maintained.



If a study involves “research” and “human subjects” as defined by [45 CFR 46](#), then investigators are required to submit an application to the CWRU IRB via the SpartaIRB system for approval prior to any study procedures beginning, including the recruitment of study subjects and the collection of data. Research studies involving human subjects for student theses and dissertations always require prior IRB approval. Data collected before approval is obtained is in non-compliance with university policy and cannot be used for research.

The IRB will review and ensure that non-exempt research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the follow review methods:

- Expedited Review
- Review by Convened IRB

## IRB ADMINISTRATION

### **What are the roles of the IRB Office?**

The IRB Office Administrators are responsible for making determinations of exemption, screening protocols for necessary components before sending to IRB member(s), answering investigator questions, facilitating IRB review of protocols, maintaining records, providing required written documentation of IRB actions. One Associate Director, IRB also serves as a member of the IRB Advisory Committee (IAC). If there are any questions about human subjects research or Case IRB procedures, please contact the IRB Office by email at [cwru-irb@cwru.edu](mailto:cwru-irb@cwru.edu) or by phone at 216-368-6925.

The federal regulations at [45 CFR 46.108](#) and the Common Rule require CWRU to provide its IRB with sufficient meeting space and to support the IRB’s review and record-keeping responsibilities. The IRB shall include the administrative personnel to manage the processing of the application to establish operating procedures to promote consistency and efficiency. The IRB Office Administrators receive mentoring and training on the job. They also participate in the CREC training program required of the IRB members and investigators. Additionally, the IRB Office Administrators attend national meetings/conferences. They also receive periodic performance evaluations at least on an annual basis by the Executive Director for the HRPP.

### **Once an application has been submitted to the IRB office, when can research begin?**

No research may be initiated until the Case IRB has given a protocol full approval with no revisions. An investigator must wait to receive this approval in writing before initiating research. Verbal approval is not acceptable. Any data collected before obtaining written approval is in non-compliance with CWRU policy and cannot be used for research purposes.

### **How does the IRB Office communicate with Investigators, Primary Contact of Protocol Submissions, and PI Proxies?**

The IRB office reviews exempted protocols and sends investigators exemption notices via the electronic IRB system. However, the full IRB reviews all studies in need of full review and one or more IRB members review all studies eligible for expedited review. When Full and Expedited reviews involve major or minor modifications to secure approval, written notification of the IRB’s action, together with the reason(s) for its decision are provided to the Principal Investigator. The results of IRB actions are conveyed in writing usually within one week of a convened IRB meeting at which the protocol was considered. Furthermore, when a primary reviewer (either through Full Board or expedited review) determines that



additional modifications or clarifications are required, these are also forwarded in writing to the Principal Investigator. All communications are sent by the IRB Administrative staff.

The investigator must respond to all IRB requests and enquiries in writing or in person. When an investigator responds to the IRB actions, these correspondences are reviewed by the IRB members to determine whether the information provided satisfies the Board's requests and the criteria for IRB approval. The information can be reviewed by expedited review (when the investigator has agreed to the changes requested by the IRB, or if the protocol is eligible for review using the expedited procedure). Otherwise, the modifications are reviewed by the convened IRB.

When the IRB disapproves a protocol, the Principal Investigator is provided with written notification for the reason(s) for the disapproval; however, a detailed critique of the protocol is not provided. The investigator is instructed to contact the IRB office with any questions and may attend an IRB meeting to discuss the study. An investigator may rewrite and submit the study as a new protocol if they wish but must take into account the Board's concerns and reason(s) for the disapproval of the protocol.

### **Are Investigators invited to IRB Meetings?**

IRB meetings are not usually open to investigators. The IRB, in rare cases, may invite an investigator to attend during part of the discussion of their protocol to respond to questions from members of the IRB or provide additional information. The investigator would not be present during the final discussion about the protocol or the protocol vote.

## ***What are the different regulatory classifications that research activities may fall under?***

Submitted activities may fall under one of the following four regulatory classifications:

- Not Human Research: Activities must meet the university definition of "Human Research" to fall under IRB oversight. Activities that do not meet this definition of are not subject to IRB oversight or review. Review the IRB Office's [WORKSHEET: Human Research \(HRP-310\)](#) for reference. Contact the IRB Office in cases where it is unclear whether an activity is Human Research.
- Exempt: Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the university, not the investigator, to determine whether Human Research is exempt. Review the IRB Office's [WORKSHEET: Exemption \(HRP-312\)](#) for reference on the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the IRB Administration's [WORKSHEET: Eligibility for Review Using the Expedited Procedure \(HRP-313\)](#) for reference on the categories of research that may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

## ***What activities fall under Not Human Research?***

Activities are not research if they do not involve a systematic approach involving a predetermined method for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing theory. Examples of activities that would not normally be considered systematic investigations include, but are not limited to training activities:





- Program Evaluation
- Trained to perform a certain technique or therapy
  - Objective of activity is to teach proficiency in performing task

Activities are not research if they do not contribute to generalizable knowledge or if the results (or conclusions) of an activity are not intended to be extended beyond a single individual or an internal program (e.g., publications or presentations). Examples of activities that are typically not generalizable include:

- Biographies
- Service or course evaluations (unless they can be generalized to other individuals)
- Services, courses, or concepts where it is not the intention to share them beyond the CWRU community
- Classroom exercises solely to fulfill course requirements or to train students in the use of particular methods or devices
- Quality assurance activities designed to continuously improve the quality or performance of a department or program where it is not the intention to share them beyond the CWRU community

**Thesis or dissertation projects conducted to meet the requirements of a graduate degree are usually considered generalizable and therefore, require IRB review and approval.**

A **cadaver** is not considered to be a human subject. Projects involving cadavers should be submitted to the CWRU IRB on a [Not Human Research Protocol \(HRP-503NHR\)](#) Template. The IRB will determine if there are other considerations that should be addressed, such as HIPAA, genetic information, communicable diseases, etc.

Any change that might disqualify the activity from a “Non-Human Subject” or “Non-Research” status must be reported to the IRB for review and verification prior to implementation.

All “Non-Human Research” is subject to all applicable institutional policies and procedures. When activities are conducted that might represent “Human Subject Research”, the activities must be submitted to the IRB for a determination. The IRB Office Administrators/Chairperson or their Designee will determine whether an activity meets the definition of “Human Subject Research.”

The IRB Office Administrators/Chair or their Designee will document the determination and its justification. If the request is determined to meet criteria for Human Research, the IRB staff will determine the appropriate level of review, communicate this to the Investigator, and guide the Investigator with the re-submission. If the request is determined to be Not Human Research, the IRB staff will send a letter documenting the determination.

### ***What activities fall under the Exempt Category?***

The federal regulations allow certain research activities involving human subjects to be exempt from IRB full or expedited review [see [45 CFR 46.101\(b\)\(1-6\)](#); [45 CFR 46.401\(b\)](#)]. However, there are restrictions for research involving children (see [45 CFR 46, Subpart D](#)); and research involving prisoners does not qualify for exempt research (see [45 CFR 46, Subpart C](#)).



Exemptions are determined or granted, rather than approved. These studies are exempt from the Common Rule (45 CFR 46). They are not, however, exempt from institutional review and approval and this research is not exempt from ethical considerations, such as the principles described in The Belmont Report. The IRB Office staff make the determination of exemption and will determine whether to require additional protections for subjects in keeping with ethical principles (e.g., requiring consent).

Exempt research fulfills the University's ethical standards, such as:

- The research holds out no more than minimal risk to subjects.
- Selection of subjects is equitable.
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- If there are interactions with subjects, the IRB determines whether there should be a consent process that will disclose such information as:
  - That the activity involves research.
  - A description of the procedures.
  - That participation is voluntary.
  - Name and contact information for the investigator.
- There are adequate provisions to maintain the privacy interests of subjects.

### ***How are Determinations Made for the Exempt Category?***

Determinations regarding whether research subject to the revised Common Rule qualifies for exempt status will be made by the Research Compliance Officer or CWRU IRB Office Administrators.

A request for determination as to whether or not a human research protocol may be considered “exempt” may be submitted electronically through the SpartaIRB system by adding a new study. Investigators may also contact the IRB staff for assistance and guidance.

Upon review of the exemption request, a determination of applicability will be made by the IRB staff, and/or a designated IRB member who is familiar with the regulations.

If the request is approved, the investigator will receive a Notice of Exemption via the SpartaIRB system. The Notice of Exemption e-letter will list the applicable exempt category under the federal regulations and a statement to indicate that the IRB must review any changes prior to implementation to determine if the study still qualifies for exemption.

If the request is disapproved, the IRB staff will indicate that the study does not meet the federal requirements to be classified as “exempt” and will be given instruction about how to proceed. Depending on the type of research, minor revisions may need to be made in order to qualify for exempt status or a new application for full or expedited IRB review will have to be submitted for reconsideration.

### ***Notice of Exemption***

If the IRB Office determines a protocol meets one of the exemption categories, a notice will be generated in SpartaIRB and sent to the investigator. Notices of Exemption include:

- Protocol number
- Protocol title
- Principal Investigator
- Exemption date
- A description of the exemption category as described under 45 CFR 46.101



- A statement informing investigators to submit addenda prior to any planned change or modification.

### ***Duration of Approval***

Continuing review is not required for research that has been determined to be exempt. CWRU studies deemed exempt do not expire. However, if investigators wish to end their exempt research, the CWRU IRB asks that they submit a Continuing Review form via SpartaIRB to close the study.

On an annual basis, IRB staff will send an email to Principal Investigators with exemptions asking if investigators remain interested in keeping their exempted study active. The emails will also serve as reminders of research responsibilities as well as a request to close the said study out if that is what the investigator wants.

### ***Modifications***

Proposed changes to an exempt study after initial IRB approval must be submitted to the IRB for review prior to implementation via SpartaIRB. Certain changes may disqualify the research from exempt status (e.g., recruiting prisoners). All proposed changes – no matter how small or seemingly benign – must be submitted via the modification form in the SpartaIRB system as a modification request to the currently approved exempt study. Investigators must fully complete the modification form and include a detailed narrative which discusses the changes that are being made, as well as include any revisions to electronic components that were affected by the change (e.g., study protocol information sheets, surveys, etc.). Investigators must upload and attach all revised or new documents that would be affected by the proposed change(s).

The IRB will review the proposed changes to determine if the project still qualifies for Exempt status. If the project is still considered Exempt, changes proposed may be implemented once the investigator receives an approval for the amendment through the SpartaIRB system. An approved modification, provided it does not change the current exemption status, would not change the fact that the exempted study in question has no expiration date. If the IRB determines that the project no longer qualifies for Exemption, the investigator will be notified accordingly. The investigator will then have to follow IRB staff instructions to submit a full application for full or expedited IRB review and approval.

### ***Certification in Human Subject Protections***

Investigators requesting a determination of exemption are required to be certified in Human Subjects Protections through the [CWRU CREC \(Continuing Research Education Credit\) Program](#).

### ***Limitations on Exemptions***

Children: Exemption #2(i) and (ii) for research involving survey or interview procedures or observations of public behavior does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed. Exemption #3 does NOT apply to research involving children. [§46.104(b)(3)]

Prisoners: Exemptions do not apply EXCEPT for research aimed at involving a broader subject population that only incidentally includes prisoners. [§46.104(b)(2)]

## *What Activities Fall Under the Exempt Review Category?*

### *Exempt Categories [45CFR46.104\(d\)](#)*

Unless otherwise required by law or a federal agency or department, research activities in which the only involvement of human participants will be in one or more of the following categories are exempt from the additional requirements of the revised Common Rule, except as specified.

**Note:** Other than Exempt Category 6, these categories do not apply to research that is also FDA-regulated.

1. Research, conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
  - (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; or
  - (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.
3. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
  - (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; or
  - (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that they will be unaware of or misled regarding the nature or purposes of the research.



4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
  - (i) The identifiable private information or identifiable biospecimens are publicly available;
  - (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
  - (iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164 ['HIPAA'], subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
  - (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
  
5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.
  - (i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.
  
6. Taste and food quality evaluation and consumer acceptance studies if:
  - (i) Wholesome foods without additives are consumed, or
  - (ii) A food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

**Please Note:** CWRU is not adopting the option for broad consent. Therefore, Exempt Categories 7 & 8 are not applicable when the CWRU IRB staff or members review research studies.





## ***What Activities Fall Under the Expedited Review Category?***

Research may be reviewed by the IRB under expedited procedures if all research activities present no more than minimal risk to human subjects and involve only procedures listed in one or more of the specific categories under [45 CFR 46.110](#).

**Expedited Review** is review of research involving human subjects by the IRB Chair, Vice-Chair, or by one or more experienced IRB member reviewers designated by the Chair from among members of the IRB.

The federal regulation in [45 CFR 46.110](#) allows for certain kinds of research involving no more than minimal risk, and for minor changes in approved research to be reviewed using the expedited review procedure.

Expedited review of research subject to the revised Common Rule will be conducted per the Federal Regulations with the following variations:

1. Research that falls within the list of categories is presumed to be minimal risk unless the IRB determines and documents that the research involves more than minimal risk. [§46.110(b)(1)(i)]
2. If the reviewer determines that the research involves more than minimal risk, it will be referred for review by the convened IRB.
3. Continuing review of research is not required for research that qualifies for expedited review unless the IRB determines that is required and documents the rationale within the IRB record

The Department of Health and Human Services (DHHS) has established a list of categories of research that may be reviewed by the IRB through expedited review [[45 CFR 46.110\(a\)](#)] categories as listed below. Under 45 CFR [46.110\(b\)](#), the CWRU IRB may use the expedited review procedure to review either or both of the following:

- Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk.

The initial and continuing review of protocols and change requests are initially reviewed by the IRB Office to determine if the proposed research meets the regulatory criteria for expedited review. If the research meets the criteria stipulated under 45 CFR 46.110(b), it is forwarded for expedited review.

## ***What are the IRB Reviewer Responsibilities when Research Activities Fall under the Expedited Review Category?***

Investigators must complete and submit a new protocol or modification form via SpartaIRB. For new submissions, the submission must include uploaded consent forms, data collection forms, recruitment materials, and all other document that are to be used in the research. For modifications, the submission must include any revised documents.

## ***What are the Expedited Review Categories?***

The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list only 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. Other qualifications that apply:

- The categories in this list apply regardless of the age of subjects, except as noted.
- 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.

- The expedited review procedure may not be used for classified research involving human subjects.
- 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.
- Categories 1 through 7 pertain to both initial and continuing IRB review.
- Some research under categories 5 and 7 may qualify for exempt status, in which case the expedited rules do not apply.

### **Category 1 – Drugs and Devices**

Clinical studies of drugs and/or devices only when one of the following is true:

- Research on drugs for which an investigational new drug (IND) application is not required
- Research on medical devices for which one of the following is true:
  - An investigational device exemption (IDE) application is not required, or
  - The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

### **Category 2 – Blood Samples**

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

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

### **Category 3 – Biological Specimens**

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

- Hair and nail clippings in a non-disfiguring manner.
- Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
- Permanent teeth if routine patient care indicates a need for extraction.
- Excreta and external secretions (including sweat).
- Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue.
- Placenta removed at delivery.
- Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
- 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.
- Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
- Sputum collected after saline mist nebulization.



#### **Category 4 – Non-invasive Data Collection**

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. Examples of such procedures include:

- Physical sensors applied 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
- Weighing or testing sensory acuity
- Magnetic resonance imaging (MRI)
- Electrocardiography (ECG or EEG)
- Thermography
- Detection of naturally occurring radioactivity
- Electroretinography
- Ultrasound
- Diagnostic infrared imaging
- Doppler blood flow
- Echocardiography
- Moderate exercise, muscular strength testing, body composition assessment and flexibility testing where appropriate, given age, weight and health of the individual

#### **Category 5 – Data Collected for Non-Research Purposes**

Collection of materials (data, documents, records or specimens) that have been or will be collected solely for non-research purposes such as medical treatment or diagnosis.

#### **Category 6 – Data from Recordings**

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

#### **Category 7 – Behavioral Research**

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.

#### **Category 8 – Continuing Reviews**

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

##### Category 8a (follow-up activities only)

- The research is permanently closed to the enrollment of new subjects;
- All subjects have completed all research-related interventions; and
- The research remains active only for long-term follow-up of subjects.

##### Category 8b (research not started)

- No subjects have been enrolled and no additional risks have been identified.

##### Category 8c (data analysis only)

- The remaining research activities are limited to data analysis.

#### **Category 9 – Continuing Reviews approved by the Full Board**



- The research is not conducted under an investigational new drug application or investigational device exemption; and
- 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.

### *What Decisions Can the IRB Make in Review of Protocol Submissions?*

The IRB may approve research, require modifications to the research to secure approval, defer research, or disapprove research:

- **Approval:** Made when all criteria for approval are met. See WORKSHEET: Criteria for Approval (HRP-314). The human subject research may commence once all other institutional approvals have been met. IRB approval is for a period of time which is noted in the approval letter. If no expiration date is noted, a periodic check-in may still be required.
- **Modifications Required to Secure “Approved Determination:”** Made when IRB members require specific modifications to the research before approval can be finalized. If the IRB requires modifications to secure approval the study team must make the requested modifications and submit them to the IRB. If the IRB determines that all requested modifications have been addressed, final approval will be issued. Research cannot commence until this final approval is received. If you do not accept the modifications, submit a response through the system justifying your disagreement with the request. Any substantive modification made outside of requested changes will void the determination and the study will again be reviewed as a whole.
- **Deferred:** Made when the IRB determines that the board is unable to approve research, and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB. If the IRB defers the Human Research, a statement of the reasons for deferral and suggestions to make the study approvable will be provided. The study team may address the issues and resubmit. In most cases if the IRB’s reasons for the deferral are addressed the Human Research can be approved.
- **Disapproval:** Made when the IRB determines that it is unable to approve research, and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision. Any further proposals would have to be part of a new submission.

The criteria for IRB approval can be found in the WORKSHEET: Exemption ([HRP-312](#)) for exempt Human Research and the WORKSHEET: Criteria for Approval ([HRP-314](#)) for non-exempt Human Research. The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found in the SpartaIRB Library.

These checklists are used for initial review, continuing review, and review of modifications to previously approved Human Research. These checklists should be used to write the protocol submission because they address the criteria for approval.

## Can The IRB Decision be Overturned?

### *Disagreeing With IRB Decisions*

Researchers may request that the IRB reconsider a decision by submitting a written response to the IRB. When submitting a request to reconsider, the researcher must provide rationale for the request, including any additional supporting documents.

Grounds for a request are limited to:

- New information not reasonably available during the IRB review/investigation
- Material failure by the IRB to follow IRB policies and procedures
- The sanction exceeds the severity of the noncompliance violations, if applicable
- The action is disproportionate to the risks to participants safety/welfare

These considerations also apply to all other submissions, including changes, continuing reviews, reportable events, and also where the IRB has suspended or terminated the research.

### *Can the HRPP Institutional Official Overturn an IRB Decision?*

No, the institutional official at CWRU cannot reverse IRB decisions that involve disapproval, deferral, suspension, or termination of a research study. However, the CWRU Institutional Official (Senior Vice President for Research) as designated by the CWRU President can disapprove an IRB approved protocol for activation or continuation at CWRU.

### *What are Special Protections for the CWRU IRB Members?*

CWRU prohibits officials, investigators, staff, students, and sponsors from attempting to or using undue influence with the CWRU IRB, any of its members or staff, or any other member of the research team to obtain a particular result, decision, or action. “Undue influence” means attempting to interfere with the normal functioning and decision making of the CWRU IRB or to influence an IRB member or staff, or any other member of the research team outside of established processes or normal and accepted methods, in order to obtain a particular result, decision, or IRB action.

If a CWRU IRB Committee member, IRB staff, Principal Investigator, research participant, or other individual feels that they has been unduly influenced (e.g., coerced to participate, approve a study, or conduct a study), a report should be made to the CWRU Research Compliance Officer via email: kav6@case.edu or phone: 216-368-0134. The CWRU Research Compliance Officer will investigate the allegation and when appropriate, take corrective actions. Appeals related to IRB policies and procedures (including investigator concerns or suggestions regarding the review process) will be reviewed and forwarded to the Institutional Official, if necessary.

## CHAPTER 3 – Health Insurance Portability and Accountability Act (HIPAA) Research and Privacy Board Processes

### What is HIPAA?

The Health Insurance Portability and Accountability Act of 1996 ("HIPAA") was written to allow for insurance portability but also as a Privacy Rule to protect the privacy and security of a person's identifiable health information. The purpose of this guidance is to provide researchers with the information they will need to comply with the Privacy Rule associated with HIPAA.

The HIPAA Privacy Rule establishes the conditions under which Protected Health Information (PHI) may be used or disclosed by covered entities for research purposes. CWRU is a hybrid entity and as such, must abide by the HIPAA Rules for the use and disclosure of PHI under its jurisdiction (see 45 CFR 160 and 164) for related purposes. CWRU and its affiliated hospitals empower their IRBs to act as Privacy Boards on behalf of each Covered Entity.

### Definitions Pertinent to HIPAA

Authorization is permission to gain access to PHI. Authorization may be obtained by signing a separate document or incorporating authorization language into a consent form.

***HIPAA (Health Insurance Portability and Accountability Act)*** – HIPAA regulates the transfer and collection of PHI between and within covered entities defined as:

1. Health care plans;
2. Health care clearinghouses, and;
3. Health care providers who electronically transmit any health information.

The Health Insurance Portability and Accountability Act (HIPAA) went into effect on April 14, 2003, to ensure the portability of insurance coverage as employees moved from job to job; increase accountability and decrease fraud and abuse in healthcare; and improve the efficiency of the health care payment process, while at the same time protecting a patient's privacy.

#### ***Covered Entity***

HIPAA applies to "Covered Entities," defined by the Privacy Rule as a healthcare provider that conducts certain transactions in electronic form, a healthcare clearinghouse, a health plan, or a business associate (person or organization) performing a function on behalf of the Covered Entity for which access to protected health information is needed.

#### ***Hybrid Entity***

CWRU is permitted to designate itself as a "hybrid entity," which allows it to apply the Privacy Rule only to those parts of CWRU that, if standing alone, would be a Covered Entity. As a hybrid entity, CWRU must designate its "healthcare components," which includes departments that provide support for healthcare components. Healthcare components at CWRU are:

- CWRU School of Dental Medicine
- CWRU School of Dental Medicine Faculty Practice
- CWRU Student Self-Insured Health Plan & Optional Dependent Medical Plan



- CWRU Employee Health Plan
- Prion Disease Pathology Surveillance Center

**Privacy Rule** establishes the minimum federal standards for safeguarding the privacy of individually identifiable health information (also referred to as protected health information (PHI)). The Department of Health and Human Services (HHS) issued the Privacy Rule in order to implement the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which required compliance as of April 14, 2003 (see 45 CFR part 160 and subparts A and E of part 164). The Privacy Rule includes the standards for an individual's privacy rights, to enable them to understand and control how their health information is used. Within HHS, the Office for Civil Rights (OCR) is authorized to implement and enforce the Privacy Rule.

**Protected Health Information (PHI)** is individually identifiable health information, including demographic and genetic data that is collected from an individual and:

1. Is created or received by a health care provider, health care entity, health plan, public health authority, employer, life insurer, school/university, or health care clearing house; AND
2. Relates to past, present or future physical or mental health or condition of the individual; or the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; AND
3. Identifies the individual or where there is a reasonable basis to believe the information can be used to identify the individual; AND
4. Is transmitted or maintained in any form or medium, whether electronic, paper or oral (see [45 CFR 160.103](#)).

**Research Privacy Board** is a review body which acts upon the HIPAA Privacy Rule's authorization requirements for use or disclosure of PHI for a specific research protocol. The Research Privacy Board's authority is limited to approval of privacy language; approval of requests for a waiver or alteration of the Privacy Rule's authorization requirements; approval for the use of PHI from deceased individuals; and review of HIPAA compliance allegations. CWRU and its affiliated hospitals empower their IRBs to act as Privacy Boards on behalf of each Covered Entity.

**Research**, as defined in the Privacy Rule, is a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 164.501).

### ***What Is the Investigator's Responsibility for HIPAA?***

Any research study involving collection or use of PHI must comply with HIPAA. It is the responsibility of the investigator to comply with HIPAA Authorization/Privacy Rule requirements, and the policies relating to use of PHI in research as outlined by the CWRU HIPAA Policies.

**Authorization** is the HIPAA equivalent of consent for use or disclosure of a person's PHI. Required elements for an authorization form include:

1. Specific description of what PHI will be used or disclosed.
2. Who may use or disclose PHI.
3. Who may receive the PHI.
4. Purpose of the use or disclosure.
5. Statement of how long the use or disclosure will continue. "No expiration date" is allowed for research purposes.
6. Right to revoke authorization.





7. Notice that the information may be disclosed to others not subject to the Privacy Rule.
8. Right to refuse to sign authorization.
9. The subject must sign the form and receive a signed copy for the authorization to be valid.

The HIPAA authorization can be a separate document from the consent form, or the required elements can be incorporated into the consent form. Authorization should be obtained in each of the following two circumstances:

1. When requesting permission from a patient to have their name, address and phone number or other health information released to an investigator for recruitment into a research study; or
2. When enrolling a subject into a specific research study to request permission to collect their PHI as related to the research study. This second circumstance occurs simultaneously with the consent process.

### ***Waiver of Authorization***

Waiver of Authorization can be obtained if the following three criteria have been met:

1. The research is no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
  - a. Adequate plan to protect the identifiers from improper use and disclosure.
  - b. Adequate plan to destroy the identifiers at the earliest opportunity.
  - c. Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity.
2. The research cannot practicably be carried out without a waiver; and
3. The research cannot be done without this specific PHI.

When applying for a waiver of authorization, the investigator must complete the "Waiver of HIPAA Authorization (HRP-600)" form, which is found in the SpartaIRB electronic system under the Library tab/Templates. Uses and disclosures of PHI pursuant to the waiver must be limited to the minimum necessary to achieve the research purpose. This means that if you use a waiver to collect PHI, you must only collect the bare minimum of information from patient records that are necessary to answer the research question.

### ***Examples of when a waiver may be utilized:***

Example 1: A researcher would like to conduct a retrospective chart review at Treatment Center X. Waiver of consent is appropriate because it is impractical to attempt to contact the many patients that a retrospective chart review entails, and the chart review is considered to be minimal risk. [NOTE: If only de-identified data are recorded, then it is not considered to be PHI, and no waiver of authorization is required.]

Example 2: A researcher has a list of patients who were involved in his previous study and would like to re-contact these patients to participate in a follow-up study. The investigator would apply for a waiver of authorization to pull medical records to find the patients' current phone numbers. The investigator will still need to use an authorization form when enrolling the subjects, but in order to obtain this PHI before contacting the patients, a waiver is required.

### ***De-Identified Data***

Health information is considered de-identified when it does not identify an individual and the health care entity has no reasonable basis to believe that the information can be used to identify an individual. Research involving de-identified data will not be required to adhere to HIPAA regulations requiring authorization.



De-identified data includes none of these 18-identifying links:

1. Name
2. Address including city, county, precinct, zip code
3. All elements of dates (except year) for dates directly linked to an individual (birth date, admission date, discharge date, date of death) [For all subjects over 89 years, all elements of dates including year that are indicative of their age cannot be used; however, age can be aggregated into a category of age 90 or older.]
4. Telephone numbers
5. Fax numbers
6. E-mail addresses
7. Social security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license number
12. Vehicle identifiers
13. Device identifiers
14. Web Universal Resource Locators/Identifiers
15. Internet Protocol address numbers
16. Biometric identifiers including finger or voice prints
17. Full face photographs and comparable images
18. Any other unique identifying number, characteristic, or code

### ***Limited Data Set***

Limited Data Sets include research that falls under HIPAA regulations but does not require researchers to obtain authorization or waiver of authorization. Researchers can collect data that retains the following types of identifiers:

- Admission, discharge and service dates
- Birth date
- Date of death
- Age (including over age 89)
- Geographic information (except street addresses) such as city, state, and five-digit zip code

Researchers using a limited data set will be able to use the data only for research purposes but may not use the limited data set to contact subjects.

### ***Recruitment of Participants***

No researcher may contact potential participants with whom the researcher does not have a clinical relationship without authorization. If a researcher wishes to recruit subjects into a study, then the researcher must request that a health care provider who does have a clinical relationship with these subjects obtain authorization from the subjects to release information to the researcher. Alternatively, the care-providing physician can give the patient the contact information about the study.

The HIPAA rule does not apply at research sites outside of the United States where individually identifiable information may be collected. Once the individually identifiable information is transferred to a HIPAA-covered facility then any individually identifiable health information becomes PHI by virtue of its being



held by a facility covered by HIPAA. Once data is transferred to a HIPAA covered component, all HIPAA regulations apply.

All investigators conducting research outside the United States must comply with HIPAA requirements for all studies unless the investigator requests a waiver of HIPAA based on criteria outline in 45 CFR 164.512. This includes when the investigator conducting research outside the United States sends PHI back to the United States in any form.

## CHAPTER 4 – Research with Existing Specimens or Data

### What Are Key Concepts to Consider Before Working With or Research Activities With Existing Specimens or Data?

- Most uses of data or specimens that include identifiers require IRB approval, though not all.
- The IRB assesses each proposal for use of existing data or samples on a case-by-case basis to determine whether they are research.
- If you are using clinically obtained samples or data from deceased individuals AND the activity is not FDA regulated, no IRB approval is required.
- Any use of specimens or data collected as part of a research study requires review from the IRB, regardless of whether identification status.

***Please Note:***

- When the research method involves obtaining coded private information or specimens, and it is not FDA-regulated, the IRB will review the research according to parameters described in the [Office for Human Research Protections Guidance on Research Involving Coded Private Information or Biological Specimens](#).
- Activities that do not involve human participants, according to the current Guidance, will be designated as such.
- The IRB should be consulted when there are plans to conduct research involving coded private information or specimens, or de-identified information or specimens collected through research.

### Definitions That Are Pertinent to Research With Existing Specimens or Data

***Identifiable*** means that data or specimens contain information or labeling that allows someone to readily ascertain the identity of the individual to whom the data or specimens belong.

***De-identified*** is a term related to HIPAA that means the data or specimens have had all of the HIPAA designated identifiers removed, but there may still be a link between the data or specimens and the identity of the individual from whom they came. This link is often a code.

- Coded data, when the code itself does not contain any meaningful, or information directly associated with the individual (such as hospital number or SSN) is considered HIPAA de-identified. However, this is NOT the same as the data being anonymous (or anonymized) and does NOT necessarily mean that the data are de-identified under Human Research regulations.

***Anonymized*** means that all identifiable information has been removed from the data or specimens and that no link remains between the data or specimens and the identity of the individual to whom they belong. The data or specimens could never again be associated with the individual by anyone.

### Terms That Help the IRB Determine When IRB Approval is Required

***Identifiable:*** A research project using identifiable data or specimens requires IRB approval because it meets the definition of Human Research.



**De-identified:** Projects using de-identified data and specimens sometimes require IRB approval and sometimes not.

**Example scenarios:**

- **Current access or not to Identifiers/Master list:**
  - When the Investigator receives the private information or specimens with no code or link that would allow an Investigator to establish identity, this would not involve human participants. For example, a publicly available, unidentifiable, non-linked cell line qualifies as not involving human participants.
  - The Investigator may receive coded private information or specimens and qualify for non-human subject if the following conditions are met:
    - The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
    - The Investigator cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain, because:
      - The key to decipher the code is destroyed before the research begins;
      - The Investigator and the holder of the key enter into an agreement prohibiting the release of the key to the Investigator under any circumstances, until the individuals are deceased;
      - The private information is received from an IRB-approved repository or data management center that includes written operating procedures that prohibit the release of the key to the Investigator under any circumstances, until the individuals are deceased; or
      - There are other legal requirements prohibiting the release of the key to the Investigator until the individuals are deceased.
- **Coded data or specimens**
  - If the data/specimens are coded AND none of the investigator and study team members have access to the identifies or master list, the project could be non-Human Research (non-HR).
  - The Data Use Agreement may have terms that include:
    - The holder of the code will not re-identify the data for the recipient; and
    - The recipient will not attempt to re-identify the data by any means.
- **A limited data set** is information from which certain identifiers have been removed, but other less obvious identifiers remain. Researchers using a limited data set will be able to use the data only for research purposes and may not use the limited data set to contact subjects.
  - Limited Data Sets include research that falls under HIPAA regulations but does not require researchers to obtain authorization or waiver of authorization. Researchers can collect data that retains the following types of identifiers:
    - Admission, discharge, and service date
    - Birth date
    - Date of death
    - Age (including over age 89)
    - Geographic information (except street addresses) such as city, state, and five-digit zip code
  - All the following HIPAA-18 identifiers must be removed in order for health information to be a limited data set:
    - Names
    - Street addresses (other than town, city, state and zip code)



- Telephone numbers
  - Fax numbers
  - E-mail addresses
  - Social Security numbers
  - Medical records numbers
  - Health plan beneficiary numbers
  - Account numbers
  - Certificate license numbers
  - Vehicle identifiers and serial numbers, including license plate numbers
  - Device identifiers and serial numbers
  - Web Universal Resource Locators (URLs)
  - Internet Protocol (IP) address numbers
  - Biometric identifiers (including finger and voice prints)
  - Full-face photographic images (or comparable images)
- The health information that may remain includes:
- Dates such as admission, discharge, service, date of birth or death;
  - City, state, five digit or more zip code; and
  - Ages in years, months or days or hours.

If the project involves a **Limited Data Set**, a Data Use Agreement (DUA) is generally required. A DUA outlines the acceptable uses and restrictions on the Limited Data Set once it is shared.

- Research using a limited data set under a DUA may be Not Human Research
- When sharing specimens, a Material Transfer Agreement (MTA) could be required.
  - This is an agreement that governs the transfer of tangible research materials between two organizations, when the recipient intends to use it for their own research purposes.
  - The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives.

**Note:** Please see the [ORTM WEBPAGE](#) to find additional information in working with the Data Use Agreement and Contracts Office and the Technology Transfer Office.

### ***Anonymized***

If a researcher is using anonymized data, generally this would be considered Not Human Research. Again, each project is considered on a case-by-case basis.

**Note:** If you are unsure whether your project requires IRB approval, please contact the CWRU IRB Office.

### ***What About Data or Samples from Decedents?***

If your study is not FDA regulated AND all data/specimens that were collected for purposed other than research are from deceased individuals, the project would be Not Human Research. This is because the HHS definition of a human subject specifies that the subject is “a living individual.” **However, if the research falls under FDA regulations, the FDA definition does not make this distinction.** Therefore, FDA regulated research with data/specimens from deceased individuals may be considered Human Research.



## CHAPTER 5 – Required Training Necessary to Conduct Human Subject Research

### Definitions Pertinent to Human Research Training

**CITI:** Collaborative Institutional Training Initiative, a web-based educational program in the ethics and protection of human subject research. May be used for both core initial certification and continuing education requirements. The program can be accessed at <https://www.citiprogram.org/>

**CREC:** Continuing Research Education Credit

**GCP:** Good Clinical Practice

**RCR:** Responsible Conduct of Research

### What Is the Continuing Research Education Credit (CREC) Program?

The CWRU IRB collaborates with the other institutional review boards, including University Hospital Cleveland Medical Center (UHCMC) and MetroHealth Medical Center in a common program for human subject protections certification. The [Continuing Research Education Credit \(CREC\)](#) program provides documented training on the protection of human participants in research and meets the requirements for human subject certification for both the National Institutes of Health (NIH) and the CWRU IRB.

### Who Is Required to Complete CREC Training?

The CWRU IRB requires that the Principal Investigator, Co-Investigators, and all study team members including students complete and maintain CREC training prior to conducting human research. This includes all team members who:

- Collect or have access to private identifiable data or PHI (Protected Health Information), and/or
- Recruit, consent human participants and/or
- Interact with potential, enrolled, or former study participants

In addition, the IRB certification requirements are applicable to research determined by the IRB to be exempt from IRB review and approval.

Although recommended, research team members listed on submissions determined “Not Human Research” will not be required to complete the IRB training requirements.

Once certified, investigators and staff must maintain valid certification by participating in on-going continuing research education programs. Certified investigators and research staff members (key personnel and/or individuals obtaining informed consent) must earn 12 CRECs ([Continuing Research Education Credits](#)) every three years to maintain their certification in human participants’ protections.

Protocols may be submitted to the IRB pending investigator certifications; however, determinations or approvals will not be issued until investigator certification is complete. If certification lapses, re-



certification must be complete before approval for study modifications and continuing reviews will be issued.

Failure to meet the requirements for human participants' protections certification means that the investigator and/or research staff cannot participate in an IRB-approved protocol. Nor can an investigator and/or research staff obtain approval for a pending protocol application. If CREC certification expires during the course of an IRB-approved protocol's approval period, then the protocol cannot be approved via continuing review. If CREC certification expires during the course of an IRB-approved protocol's approval period and an investigator requests a modification, then the modification cannot be approved.

IRB Members and alternates must be CREC-certified and must maintain their certification while serving on the IRB.

## What Happens If You Are Previously Certified at Other Institutions & Now Will Conduct Research at CWRU?

An individual may have current training in the protection of human participants in research from another institution. If individuals are from the following institutions, the CWRU CREC Program will honor their certification, if complete and current:

- University Hospitals
- The MetroHealth System
- VA Northeast Ohio Healthcare System

Note: if previously certified through the Cleveland Clinic, individuals may need to complete additional CREC modules. Please contact [crec@case.edu](mailto:crec@case.edu)

## Can Investigators at Other Institutions Be Added to CWRU IRB Protocols?

Consultation with the IRB is required before adding external investigators or researchers to a protocol submission due to regulatory factors that are required to be addressed and followed.

If an external study team member's institution has an IRB, then their IRB is required to cover the Human Research activities they will be engaged in for the study. Additionally, Investigators at other institutions, who are named on a CWRU IRB study must be certified in human subject protection following their institution's or CWRU's Policy. Proof of certification from the investigator's institution must be submitted to the IRB.

## What Are the Initial CWRU Certification Conditions?

Successful completion of the Collaborative Institutional Training Initiative (CITI) course is the only way to enter the Case Western Reserve University's CREC program. Passing the course with a cumulative score of 85% is required to enter the CREC Program. Any of the following training groups for research faculty, staff, and students may be taken to meet the initial certification requirement:

- Group 1 \*Biomedical Research
- Group 2 \*Social & Behavioral Research



\* The faculty member, staff or student should select the course that is most relevant to their research or discipline.

The following link provides additional information and the direct link to the CITI Online Education Program: <https://www.citiprogram.org/index.cfm?pageID=14>

Specific instructions for completing the CITI training registration can be found at the following link: <https://case.edu/research/faculty-staff/education-and-training/continuing-research-education-credit-crec>

Initial certification lasts for three years. The only option for initial certification is the CITI Online Training course. All training is done online and can be completed in multiple sessions. See the [Continuing Education Options](#) document for more information.

## What Are Opportunities to Earn CREC Credits to Renew a CREC Certificate?

Once initial certification has been received, investigators, key personnel, and other members of the research team must accumulate 12 Continuing Research Education Credits (CRECs) every three years to be re-certified. Certification is required for as long as they are involved in human subject research. For continuing education, investigators may combine CRECs from the Options below to meet the required 12 CRECs for re-certification. Responsible Conduct of Research (RCR) training is NOT valid for CREC. Passing the course with a cumulative score of 85% is required for each option in order to earn CREC. There are multiple options for earning CRECs for re-certification:

### Option 1: CITI Courses

CITI updates their course modules with the most current information available. Those wishing to earn continuing credits for recertification may do so every three years. The corresponding credits are included.

### Option 2: CITI Webinars

CITI updates their webinars with the most current information available. Those wishing to earn continuing credits for recertification may do so every three years. The corresponding credits are included.

### Option 3: CREC Recorded Seminars and Quizzes (1 - 4 CREC per seminar)

This option allows participants to view some of our past CREC seminars and take an online quiz for credit.

### Option 4: CREC Seminars

The CWRU Office of Research Administration offers a variety of seminars each semester that have been pre-evaluated for CREC. The number of credits is listed if the seminar qualifies for CREC. Our online system allows individuals to see a listing of upcoming seminar descriptions and register to attend the events.

### Option 5: External Human Subjects Training

The CWRU Office of Research Administration conducts research in order to provide free CREC-approved external human subjects training such as the Office for Human Research Protection (OHRP) and the Program for Readability in Science and Medicine (PRISM). This training is available on the [CREC webpage](#).

## What Is a CREC Credit Application?

Appropriate education and training activities that are not sponsored by the Office of Research Administration (such as departmental or external seminars and conferences) may also qualify for CREC. CREC are awarded based on the amount of time dedicated specifically to a discussion of the ethical conduct of human subjects' research. An individual may apply for credit for a group or for him/herself. The Office of Research Administration will accept applications, with appropriate supporting documentation, prior to the event or upon its completion. Complete the [CREC Credit application](#) and attach:

- Program agenda
- Seminar handouts
- Sign-in attendance sheet (if applicable)
- Submit the application to [crec@case.edu](mailto:crec@case.edu)

## When Is Good Clinical Practice (GCP) or Responsible Conduct of Research Training Required?

National Institute of Health (NIH) and many industry sponsors require the investigators and staff involved in the conduct, oversight or management of funded studies to be trained in Good Clinical Practice (GCP) every three years, consistent with the principles of the International Conference on Harmonisation (ICH) E6. For more information on this requirement, see [Good Clinical Practice Training | grants.nih.gov](#)

GCP for Clinical Investigations of Drugs and Devices (FDA) training is available as an optional course through the CITI program. GCP for Social & Behavioral Research is available through the Society for Behavioral Medicine at this link: [Good Clinical Practice eCourse | SBM - Society of Behavioral Medicine](#)

The U.S. National Science Foundation requires the investigators and staff involved in the conduct, oversight or management of NSF-funded studies to be trained in Responsible Conduct of Research (RCR) every three years. For more information see [Responsible Conduct of Research | Office of Research and Technology Management | Case Western Reserve University](#)

RCR training is available as an optional course through the CITI program. There are four options to choose from: Biomedical Responsible Conduct of Research, Social and Behavioral Responsible Conduct of Research, Physical Science Responsible Conduct of Research, and Humanities Responsible Conduct of Research. Investigators should choose the option that most closely reflects their area of research and advise their study team members of the most appropriate module option.

The Principal Investigator is required to ensure that the training requirements of the sponsor have been met. They should verify that GCP, RCR, or other sponsor-required training has been completed by all their study team members. Once training has been completed, please forward the completed certificates or training documentation to [crec@case.edu](mailto:crec@case.edu)

## What Is the NIH Training Certification Letter Template?

Investigators who need training documentation for NIH grant submissions should contact the Continuing Research Education Credit (CREC) Program at 216-368-5963 or [crec@case.edu](mailto:crec@case.edu)

## CHAPTER 6 – Principal Investigator and Study Team Member Responsibilities

### Who Can Be the Principal Investigator of an IRB Protocol Submission?

The Principal Investigator (PI) of all protocol submissions submitted to the IRB **must be a CWRU faculty member**. The definition of a CWRU faculty member includes:

- CWRU Board of Trustees appointed Faculty, who are eligible for benefits
- CWRU Board of Trustees appointed Faculty at affiliate hospital (CC, Metro, UH, and VA) with research funding managed by CWRU
- CWRU Board of Trustees appointed Faculty/Clinical Faculty (CC, Metro, UH, and VA) conducting research to benefit CWRU Students

Some exceptions can be made for individuals who meet the following criteria:

- Post-Doctoral Scholar/Fellow with independent funding
- Research Scientist/Senior Research Associate/Research Associate; CWRU benefits eligible- with approval from Department Dean/Chair or Vice President of Unit
- Other Staff Positions- with approval from Department Dean/Chair or Vice President of Unit

**Please note:**

- Faculty members who hold faculty positions at another University or outside entity and have an Adjunct position at CWRU cannot act as the Principal Investigator but can be a Co-Investigator on the protocol.
- Since a Professor Emeritus is a retired faculty in recognition of meritorious service to CWRU, they are no longer an active faculty member. The Emeritus status signifies retirement from full-time service at CWRU. Therefore, they cannot act as the Principal Investigator but can be a Co-Investigator on the protocol.
- Even if a study is student-driven, students cannot act as Principal Investigators; they can only be listed as a co-investigator or research staff/assistant. This applies to all levels of students, undergraduate and graduate.

If the Principal Investigator is not CREC-certified, another CWRU faculty member who is CREC-certified must be identified as the new Principal Investigator. It is the Principal Investigator's responsibility to ensure that all study team members (faculty, staff and students) working with identifiable data are properly trained and CREC-certified. The responsibilities of the primary/responsible investigators, when conducting human subject research, include compliance with:

- Department of Health & Human Services (DHHS) regulations governing human subject protections as outlined in the CWRU Federalwide Assurance (FWA) with the DHHS Office for Human Research Protections (OHRP). As part of this agreement with the federal government, CWRU commits to following the Terms of Assurance (45 CFR 46). Read The Terms of Assurance here: [FEDERALWIDE ASSURANCE \(FWA\) FOR THE PROTECTION OF HUMAN SUBJECTS | HHS.gov](#)
- CWRU IRB policies and procedures
- State and Local laws and regulations

## What Are the Responsibilities of a Principal Investigator?

The Principal Investigator is ultimately responsible for the conduct of the study, for assuring compliance with current federal, state and local laws and regulations and IRB requirements for protecting human research participants.

Detailed Responsibilities of the PI include the following:

**1. Ensure that all Human Research receives IRB Approval in writing or a Determination of Exemption before the research starts.**

Investigators may not initiate research involving human participants without prior IRB review and approval. If data are collected for non-research purposes and an investigator later finds that the data could contribute to generalizable knowledge, the investigator must submit a proposal to the IRB for review and approval prior to research analysis, publication or presentation of the data (e.g., thesis, dissertation, journal article, poster session, public speech or presentation, or project report). It is in the investigator's best interest to consider carefully the likelihood that he or she will want to use data for research purposes in the future, and to seek IRB approval prior to commencing the work.

The implications of engaging in activities that qualify as Human Research without obtaining prior IRB review and approval are significant. Results from such studies may not be published or presented unless IRB approval had been obtained prior to collecting the data. To do so is in violation of CWRU IRB Policy and the investigator would be classified as non-compliant. It is also against CWRU IRB procedures for a student to use human subject research data, which was collected without IRB approval/determination, to satisfy thesis or dissertation requirements. Investigators should seek IRB assistance when in doubt about whether proposed research requires IRB review.

Investigators must comply with all IRB decisions, conditions, and requirements and ensure that protocols receive timely continuing IRB review and approval.

**2. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations.**

Investigators should incorporate into the research plan a plan to ensure the just, fair, and equitable recruitment and selection of participants. When some or all the participants are likely to be special or vulnerable populations, such as children, prisoners, pregnant women, students, mentally disabled persons, or economically or educationally disadvantaged persons, the study plan should include additional safeguards in the protocol to protect the rights and welfare of these participants. The investigator should ensure that the language in the consent form is consistent with that in the protocol/study plan.

**3. Develop a research plan that is scientifically sound and minimizes risk to the study participants.**

Investigators should ensure that the research plan includes adequate provisions for:

- Monitoring of participants and data to ensure the safety of participants
- Protecting the privacy interests of participants

The study plan should contain adequate provisions to protect the confidentiality interests of participants, including an information security plan that considers the collection, re, maintenance,





analysis, and transmission of data, biospecimens and other identifiable information. The investigator should have a procedure to receive questions, complaints, or requests for additional information from participants and a process to respond appropriately. All unanticipated problems, deviations, complaints, non-compliance, suspensions, terminations, and any other events must be reported to the IRB per CWRU policies, especially if information becomes available that suggests a change to the potential risks or benefits of the research.

**4. Have sufficient resources necessary to protect study participants, including:**

- Access to a population that would allow recruitment of the required number of participants
- Sufficient time to conduct and complete the research
- Adequate numbers of qualified study staff
- Adequate facilities
- Necessary equipment
- A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability
- Availability of medical, psychological, or other support that participants might require during or as a consequence of their participation in the research

**5. Complete financial, contractual, and institutional approval requirements before the research begins.**

Investigators may not initiate research without executing all federal and state requirements, as well as all agreements and prerequisites set forth in a grant or contract that is to be completed prior to the conduct of research. The completion of all financial and contractual obligations includes, but not limited to, the following: ensuring appropriate funding is available to support the proposed research, obtaining budget approval, execution of the contract, an attestation of clinical trial qualifying status, ensuring a coverage analysis is completed, and ensuring that all necessary and appropriate contracts between CWRU and other parties are executed prior to the conduct of the study.

Investigators must ensure that all research involving human participants is reviewed by other experts (scientific review) and CWRU components and committees as applicable to the research. This includes filing an annual conflict of interests certification disclosure form for the investigator and all study staff.

**6. Conduct study in accordance with the ethical principles in the Belmont Report and the IRB-approved protocol and consent.**

The Principal Investigator must not institute any changes to the IRB-approved protocol and/or consent form document without first obtaining IRB approval for such changes (i.e., research instruments/questionnaires, recruitment materials etc.). If the Principal Investigator is conducting sponsored research, the study sponsor must also be notified of an investigator's intent to modify the protocol or consent form. **In rare instances, an investigator may deviate from the protocol without first notifying the IRB in order to eliminate an immediate hazard to a study participant. Any such protocol deviations must be promptly reported to the IRB via a protocol deviation form via the SpartaIRB electronic system.** Failure to comply with this requirement can result in an allegation of non-compliance. Documentation surrounding the event should also be placed in the research record and the medical record if applicable.



**7. Personally conduct or supervise the study.**

Principal Investigators may delegate research responsibility; however, they must maintain oversight and they retain ultimate responsibility for the conduct of those to whom they delegate responsibility. It is the responsibility of the Principal Investigator to inform all study staff including co-investigators, research nurses, coordinators, research assistants, etc. about the protocol and consent form. The Principal Investigator is ultimately responsible for the conduct of the study. It is the responsibility of each investigator to assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified under the laws of Ohio and the policies of CWRU to perform them.

Every member of the research team is responsible for protecting participants in research. Co-investigators, study coordinators, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures, adhere rigorously to all protocol requirements, inform investigators of all serious and unexpected adverse reactions or unanticipated problems involving risk to participants or others, oversee the adequacy of the informed consent process, and take whatever measures are necessary to protect the safety, rights, and welfare of participants. Regardless of involvement in research, each member of the research team is responsible for notifying the IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware, whether or not they are directly involved in the research.

The Principal Investigator should assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based and assure that all persons assisting with the research are adequately trained and informed about the protocol and their specific duties and functions. When delegating authority, the investigator should provide all co-investigators and research staff with a copy of the current research protocol and consent form and fully inform them of:

- Study procedures (including modifications to the protocol)
- Informed consent/assent requirements and process
- Potential risks associated with study participation and the steps to be taken to prevent or minimize these potential risks
- Data and safety monitoring plan(s)
- Adverse event reporting requirements
- Data and record-keeping requirements
- Current IRB approval status of the study

**Please note:** It is the responsibility of the PI to assure and document that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed, otherwise qualified, appropriately trained or credentialed to perform them, and listed on the IRB-approved protocol's study team member list.

- In addition to assuring that the site and facility are trained and prepared to initiate and implement the research, documentation of such training must be obtained and maintained.
- The Principal Investigator must also ensure that, if the protocol lists collaborating investigators at another institution, appropriate IRB approval for the study has been obtained at the other institution.



- It is also the responsibility of the Principal Investigator to be aware of any conflict of interests for any members of the study team.

**8. Recruit participants in an ethical manner.**

The recruitment of participants must respect the research participant's right to privacy and data confidentiality. An investigator should not contact their own patients, clients, or students unless the investigator has obtained the proper IRB approval and if the investigator has provided the IRB with a clear and thorough plan to prevent coercion and undue influence, for example, by having a department assistant recruit and consent the investigator's students (investigator is not in the classroom), and then retain the consent forms until after final grades have been completed.

**9. Ensure that the requirements for obtaining informed consent are met.**

The Principal Investigator for an IRB-approved protocol is ultimately responsible for the conduct of the study, including the entire informed consent process and the instruction and oversight of individuals who may be involved in this process. It is the Principal Investigator's responsibility to oversee the informed consent process, making sure that each potential participant fully understands the purpose of the research, the research procedures, the potential risks of study participation, and their rights as a research study volunteer. No human subject may be involved in research prior to obtaining their consent or, if approved by the IRB, obtaining consent/permission from their legally authorized representative unless a waiver of the requirement has been approved by the IRB. The Principal Investigator is also required to include appropriate additional safeguards in the study to protect research participants who are likely to be vulnerable to coercion or undue influence. It is the Principal Investigator's responsibility to assure that potential participants have the cognitive ability to give consent. If the responsible investigator cannot determine cognitive abilities, they are responsible to find someone with the appropriate qualifications to make that determination.

The Principal Investigator does not have to obtain consent personally. The Principal Investigator may delegate this authority to study team members. The requirements for consent designees include:

- They must be listed in the IRB protocol and approved as a person who may obtain consent.
- They must be CREC-certified.
- These individuals must be knowledgeable about the study and capable of answering study-related questions posed by the potential subject.

The Principal Investigator must ensure that each of these requirements are met and documented prior to the designee obtaining consent. If this responsibility is designated to a co-investigator, this should be clearly described in the protocol and IRB application.

**10. Maintain a Protocol File/Regulatory Binder of Human Research project documents.**

The Principal Investigator must maintain documentation of research regulatory documents and other essential documents of the Human Research project. For more information see the [CWRU Regulatory Binder Guide](#). At minimum, the regulatory file/binder must include the following items:

- All versions of the IRB-approved protocol
- A copy of all IRB approvals and acknowledgements, including new protocol approvals, modifications, continuing reviews, reportable new information, and IRB correspondence
- Any sponsor documentation, including but not limited to (as applicable) a copy of the grant application, funding agreement, contract, scope of work, and sponsor correspondence
- Study team contact information, credentials, and training



- Copies of all versions of all study instruments
- Copies of all versions of consent/assent forms with the IRB stamp and expiration date
- Copies of all advertisements, flyers, or recruitment phone/email scripts
- Documentation of adverse events, protocol deviations, unanticipated problems, and participant complaints
- Screening, enrollment, blinding, and randomization procedures and logs
- Study monitoring procedures and logs, including (as applicable) DSMB reports, internal data safety and quality procedures, and site monitoring logs
- Additional important documents to include in the regulatory file (as applicable)
  - Laboratory documents including reference values and manuals
  - Biological specimen records
  - Drug and Device records including Investigator's Brochure, IND or IDE applications, package inserts, and drug or device accountability logs

**11. Comply with Federal and Institutional time periods for record retention.**

The Principal Investigator is required to retain records associated with a human subject research project depending on contractual agreements, funding source requirements, or regulations. The data stored must be kept in a secure, protected manner. If electronically stored, the investigator is to take all precautions, for instance using secure application environments, such as CWRU's Box or CWRU's REDCap.

**12. Respond to participants who have an adverse event.**

In order to alleviate the consequences of an adverse event, the Principal Investigator must ensure that participants who have suffered an adverse event associated with research participation be directed to receive adequate care as reflected in the informed consent document.

**13. Keep participants fully informed of any new information.**

The Principal Investigator must ensure that research participants are kept fully informed of any new information that may affect their willingness to continue to participate in the study.

**14. Provide timely reports to the IRB as required.**

Any protocol deviation must be reported via Sparta IRB immediately upon learning of the deviation. The Principal Investigator must respond promptly to all requests for information or materials solicited by the IRB, including the timely submission of the research study for IRB continuing review.

**15. Make records available for inspection.**

Investigators are required to make research records available for audit by the CWRU IRB, CWRU HRPP Office, other CWRU Department as required by the IRB and institutional policies, the Office for Human Research Protections (OHRP), and any other accrediting bodies (e.g., AAHRPP).

**16. Protect subject privacy and maintain data confidentiality.**

It is the responsibility of the Principal Investigator to provide a subject privacy and data confidentiality plan in the research protocol for IRB review and approval. The plan must describe how the Principal Investigator and study team will ensure respect for subject privacy during research interactions and how confidential information will be protected from improper use and disclosure. Discussion of maintenance of subject identifiers or a plan to destroy identifiers at the earliest opportunity consistent with the appropriate conduct of the research must be included. Assurances must be provided that confidential



(private) information is necessary for the conduct of the research and that this information will not be re-used or disclosed to any other person or entity without written authorization by the subject.

**17. Document and address participant complaints/concerns.**

The Principal Investigator is responsible for providing contact information in the consent form to allow participants an opportunity to express complaints or concerns about study procedures or participation. Contact information for the study staff and for the CWRU IRB must be included in the consent form. Complaints received by the IRB, the Office of Research Administration, and/or the University Compliance Office will be investigated by the Executive Director for the HRPP, and the results reported to the IRB and the Associate Vice President for Research.

As referenced in item 10 above, the Principal Investigator is required to retain documentation in the protocol file/regulatory binder of any complaints or concerns and their resolution. Serious complaints involving subject rights or welfare, or integrity of the research study should be brought to the attention of the IRB when they occur, and all other complaints should be reported at the time of continuing review or annual check-in.

***What are the PI's responsibilities when receiving a participant complaint, concern or question?***

It is the right of research subjects to provide input, complain, voice a concern, or ask a question about a research study and to have the complaint, concern, or question resolved in a timely manner.

The CWRU IRB Office recognizes that all research subjects have the following rights:

1. Subjects should know that taking part in a research study is always a choice.
2. Subjects have the right to know the purpose of the research.
3. Subjects should be told about every procedure they will need to follow and that they can ask questions at any time during the study.
4. Subjects should be told of any possible risks, side effects, or problems from being in the study.
5. Subjects should be told of any possible benefits of being in the study.
6. Subjects should be told whether there are costs of being in the study and whether they will be paid for their participation.
7. Subjects should be told who will see information collected about/from them and how it will be kept confidential.
8. Subjects should be told about any other choices available to them other than being in the study. Alternatives must be presented if they exist.
9. Subjects should be told if medical care is available and who will pay for such care if injuries occur to them as a result of the study.
10. Subjects have the right to decline participation or withdraw from a study at any time for any reason.

Complaints, concerns, or questions may be raised by research subjects (past, present and potential), family members, designated spokespersons or anyone interested in research to the CWRU IRB phone, in writing or in person. IRB-approved consent documents include information for contacting the Principal Investigator and the CWRU IRB office should the subject have questions about the subject's rights and responsibilities and/or to report research-related problems. Each CWRU Office of Research Administration webpage includes the opportunity to provide feedback, input, and





suggestions. CWRU also implements an Integrity Hotline, which is managed by an external entity that allows for reporting of any complaints about university processes.

***Procedures the PI should take to Address the Complaint, Concern or Questions***

1. The Principal Investigator will address complaints, concerns, or questions received from subjects or others as quickly as possible.
  - a. If the complaint/concern of a subject or others indicates an unanticipated risk or a change in the risk/benefit ratio associated with the study or the complaint/concern cannot be resolved by the Principal Investigator, it must be reported to the IRB as soon as the Principal Investigator becomes aware of the issue.
  - b. If the complaint/concern does not indicate an unanticipated risk or a change in the risk/benefit ratio associated with the study or the complaint/concern can be resolved by the Principal Investigator, the information associated with the complaint/concern will be included as part of the continuing review submission for review by the IRB. However, investigators are encouraged to contact and work with the IRB Office.
2. The Principal Investigator is responsible for ensuring the IRB-approved consent documents contain accurate information for contacting the Principal Investigator should the subject have questions or research-related problems and contact information for the IRB should the subject have questions about the subject's rights as a research subject or to report research-related problems.

## What Are Additional Basic Responsibilities of the PI During the Conduct of the Study?

1. Submitting an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest
2. Ensuring that no study personnel accept or provide payments to professionals in exchange for referrals of potential participants (i.e., "finder's fees.")
3. Ensuring that no study personnel accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment (i.e., "bonus payments.")
4. Contacting the HRPP Office if a study has been selected for an FDA or OHRP audit.
5. Ensuring accountability of Investigational Drugs, Devices, or Biologics
6. Posting one IRB-approved version of a consent form that has been used to enroll participants on a public federal website designated for posting such consent forms after recruitment closes and no later than 60 days after the last study visit if your study is a clinical trial.
7. Any study meeting the definition of a Clinical Trial (or otherwise required to register) must register on [ClinicalTrials.gov](https://clinicaltrials.gov) in accordance with the policies governing use of that site. For more information, please review Chapter 27- Overview of ClinicalTrials.gov Records.
8. Maintaining additional requirements of various federal agencies in Chapters 21-25 (these represent additional requirements and do not override the baseline requirements of this section).

## Who Can Submit a New Protocol Submission to the IRB?

The PI, or designee (PI Proxy), is to complete the New Study SmartForm in SpartaIRB and attach all necessary documents. First, the completed protocol submission should be submitted for department scientific review (DSR). Once the department has completed their review, the PI must submit the study to the IRB by selecting "Submit." The PI should maintain electronic copies of all information submitted to the IRB in case revisions are required.





Before submitting the research for initial review, the PI must verify that:

- They have reviewed the protocol and acknowledge their responsibilities as Principal Investigator.
- The information in this submission accurately reflects the proposed research.
- They accept responsibility for assuring adherence to all applicable Federal, State, and Local research regulations, laws, and policies in carrying out this research.

## What Are the Responsibilities of the Study Team Members?

Co-investigators, study coordinators, research assistants, students, and all other research staff have a strict obligation to comply with all IRB determinations and procedures, to adhere rigorously to all protocol requirements, to inform investigators of all serious and unexpected adverse reactions or unanticipated problems involving risk to participants or others, to oversee the adequacy of the informed consent process, and to take whatever measures are necessary to protect the safety, rights and welfare of participants. The research team must be licensed, or otherwise qualified, and appropriately trained and/or credentialed to perform research tasks.

Regardless of involvement in research, each member of the research community is responsible for promptly notifying the IRB of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware, whether or not they are directly involved in the research.

All Investigators are required to promptly (but in no case later than 48 hours) report to the CWRU Human Research Protection Office:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections,
- Any litigation, arbitration, or settlements initiated related to human research protections, and
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the Organization's HRPP.

Investigators should not directly report any of these incidences outside of CWRU, unless required by law or to protect the immediate safety of a human subject. The CWRU HRPP Office will report all incidents that are required to be reported as required by applicable law to the FDA, HHS, or AAHRPP.

## What Are the Requirements for Student-Driven Research?

In order to ensure adequate oversight of student-led research:

- The faculty member of the student is required to be assigned as the Principal Investigator of the protocol and submit the protocol submission to the CWRU IRB (after the Department Scientific Review is completed) and any subsequent changes made to the submission for the IRB review and approval/determination process.
- The student can create the study in the SpartaIRB system and be listed as a Co-Investigator on the Study Team Table of the SmartForm.



## What Are the Faculty Member Advisor Role & Responsibilities of Student-Driven Research?

A faculty member advisor is ultimately responsible for the conduct of research for student-led research studies. In order to serve as the Principal Investigator on CWRU IRB protocols submission, the faculty member must meet the eligibility requirements of a Principal Investigator outlined on page 38, [Who Can Be the Principal Investigator of an IRB Protocol Submission?](#)

In submitting the protocol submission in the SpartaIRB system, the faculty member is required to assure the IRB of the following terms:

1. They assume the responsibilities required to oversee the conduct of the research, prevent harms and foster benefit to participants;
2. Any changes in the research project, adverse events, or incidents which may affect the conduct of research will be reported to the IRB;
3. The proposed research study has been thoroughly reviewed;
4. The topic and design of the study are appropriate for student research;
5. The student-investigator has the necessary experience and training to conduct the research;
6. Meetings with the student-investigator will occur on a regular basis to monitor study progress; if the study procedures are carried out in a location away from the University or regular channels of communication are not feasible, alternate arrangements have been made to continue communication with the student-investigator;
7. The student-investigator will promptly report any unanticipated problems and a Reportable New Information (RNI) submission via the SpartaIRB system will be submitted to the IRB;
8. The student-investigator will adhere to all requirements for continuing review and annual check-in;
9. If the student-investigator leaves the University, the faculty member is required to provide all necessary documents for terminating the study or continuing review/annual check-in; and
10. If the faculty member will not be available to continue as the PI of the study, they will arrange for an alternate faculty advisor to assume the above responsibilities and advise the IRB of this change.

## Who Is Required to Complete a Conflict of Interests Disclosure Form?

All investigators and study team members (involved in the design, conduct, or reporting of research) are required to disclose financial interests:

- On submission of an initial review.
- At least annually as part of the COI Office requirement.
- Within 30 days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

The CWRU IRB has the final authority to decide whether the interest and its management, if any, allows the research to be approved.

Any failure to appropriately report research related Conflict of Interests per CWRU's COI Policy may be considered non-compliance. The COI Committee will follow their processes and policy to investigate and address the incident.

Failure to appropriately document a conflict of interests within an IRB submission, or failure to follow an approved management plan may be considered non-compliance. These instances will be considered by the



IRB and referred to the Quality Improvement Program for education and the COI Committee and Senior Vice President for remediation. The Human Research Protection Program Office will work closely with the COI Office.

- Any investigation into possible failure to comply with Conflict of Interests policies and procedures will include education regarding those policies and procedures.
- Within 30 days of a substantiated instance of non-compliance with Conflict of Interests policies and procedures, a formal education will be provided to the Investigator.

## What Are the Steps to Change the Principal Investigator on an Active IRB Protocol?

Changes of PI often prompt changes to other parts of the study. Review all consent/assent forms, recruitment materials, and other documents to make certain they have been updated to reflect the change. The current PI may transfer responsibility to a new PI by creating a Modification in the SpartaIRB system and selecting “Other parts of the study” as the modification scope. This will “unlock” the section of the application that will allow the update of the PI and any other related study materials. The current PI must submit the modification. The new PI will be able to submit after the modification has been reviewed and approved by the IRB.

## Principal Investigator CWRU Departure

When a Principal Investigator is leaving CWRU, whether through retirement, change of employment, sabbatical, or other mechanism, the PI is responsible for closing, transferring, engaging a Reliant Review for active studies (see below: *What are the 4 options the PI has to handle active IRB Protocols before leaving CWRU?*).

In order to ensure compliance with applicable laws and Institutional policies, faculty, the PI, or a study team member should notify the CWRU Executive Director for HRPP (cwru-irb@case.edu) when a PI is leaving CWRU, at least 60 days before departure. Once the CWRU IRB Office is notified that an investigator is leaving CWRU, an email will be sent to involved parties documenting the impacted studies and will work with the PI and study team(s) to discuss the status and plan for all open studies, existing data, and records.

## *What are PIs’ responsibilities before leaving CWRU?*

Once the CWRU IRB Office is notified that an investigator is leaving CWRU:

- The departing investigator is required to develop a plan for current research before they are no longer employed by CWRU.
- The departing investigator is not permitted to begin any new research without first speaking to an IRB Administrator about the plan for continued oversight.
- The CWRU IRB Office will send a notice, and a follow up email will be sent to involved parties document the impacted studies.
- If the exit date is approaching or the individual has already left CWRU without a transition plan, the Executive Director for HRPP will be notified.
- When study teams do not appropriately or timely respond to IRB Office communications, the matter will be escalated to the Associate Vice President for research, the relevant Department Chair, and the IRB, respectively.



- The IRB will assess whether it is necessary to suspend or terminate the study to ensure subject safety.

### ***What are the 4 options the PI has to handle active IRB Protocols before leaving CWRU?***

Faculty members have four options to handle their active IRB protocol(s) before they leave the University:

1. Submit a study closure to the IRB to completely close the study without plans to transfer or continue the study.
2. Submit a study closure to the IRB to close the study at CWRU and transfer the project to the new institution.  
***Please note:*** *Data and materials collected under research protocols belong to CWRU and may not be taken without prior approval / contracts in place.*
3. Keep the study open at CWRU and at the new site.  
***Please note:*** *A Reliance Review Agreement may need to be put in place.*
4. Keep the study open solely at CWRU and submit a modification to the IRB to designate a new PI.

If a PI leaves the institution without implementing one of the above four options, a notice will be sent to the Department Chair of the former faculty member, the PI Proxy, Primary Contact, and Study Team Members that the study is being administratively closed. **Best practice is to submit a study closure form or PI change modification at least 30 days before departure.**

In all cases, a plan for the sharing and storage of all study-related datasets and documents should be in place before the PI leaves. As applicable, information on ClinicalTrials.gov should be updated, including transfer or closure of the record(s) if the PI is designated as the Responsible Party.

### ***What happens if a PI goes on an unexpected Leave of Absence or departs from CWRU without transferring responsibility for their studies?***

Not all transitions can be anticipated. If, due to a leave of absence, a PI is temporarily unable to perform these duties, they should delegate responsibilities to qualified study team members. A leave longer than 3 months should prompt a formal transfer of the PI role for the study. Alternatively, the study team can place the study on administrative hold (via a submission to the IRB) until the delegation log is updated and/or a new PI is identified.

If a PI goes on an unanticipated leave (longer than 3 months) or there is an abrupt departure from the University or one of our affiliated institutions, follow the steps below to request changing the PI.

- The Department Chair/Dean is required to prepare a letter or email message to the IRB (cwru-irb@case.edu) explaining the circumstances of the leave, identifying the current PI and study number, and naming the new PI.
- A current member of the study team prepares the modification in the SpartaIRB system to change the PI and update, as needed, any study documents.
- The study team member will be able to complete all necessary steps except submitting to the IRB. Therefore, the study team member is required to send an email to the IRB (cwru-irb@case.edu) with the modification number associated with the request to change PI and the letter from the

department head. Once the request is received, an IRB Office Administrator will temporarily give the study team member the PI Proxy role to submit the modification on the behalf of the new PI for review. IRB staff will add a comment in the system to notify the Primary Contact that the modification was submitted. If the study does not include additional staff members or a primary contact, please contact the IRB. **Please note that this process is only for use when the PI's departure is both sudden and unanticipated.**

- If there is no appropriate replacement for the PI and the department wishes to close the study, a member of the study team may complete the closure request. Upload with the submission a letter from the department head indicating the PI is no longer affiliated with CWRU, study activities are completed, and the study should be closed. Email [cwru-irb@case.edu](mailto:cwru-irb@case.edu) with the submission number and a request for an IRB Office Administrator to administratively submit.

## When Is a Study Administratively Discarded Due to Lack of Response?

In order to ensure protocols are reviewed in a timely manner, it is expected that the Principal Investigator responds to requested changes (including clarifications requested and modifications to secure approval) within 30 days.

- Proposals that are not returned to the IRB within 60 days will be reminded of a needed response.
- If after 90 days of the initial request the Principal Investigator has not responded to the request for changes, the IRB protocol will be administratively discarded.

**Please note:** If a protocol is administratively discarded, a new study submission must be created if the PI or study team wishes to move forward with submitting the research study to the IRB.

## For Protocols Reviewed by the Full Board

If a protocol has been given contingent approval with a request for minor changes or has been deferred, a written letter outlining the required changes or reasons given for the action will be sent to the investigator.

- The investigator has 90 days from the time of the IRB meeting at which the protocol was considered to respond in writing to the changes required by of the IRB.
- If the investigator does not respond in writing within 60 days from the time of the IRB meeting, a reminder will be sent.
- If the investigator does not respond in writing in 90 days, the protocol will be closed by an IRB Office Administrator.
- A written notice of study application closure for lack of response will be sent to the investigator and, if applicable, primary contact and/or PI Proxy and placed in the study history.
- If the investigator wishes to seek approval for the study after closure, a new protocol submission must be completed, submitted to the IRB via the SpartaIRB system, and reviewed and approved by the IRB.
- If there are unusual circumstances that prevent a timely response to requested changes, the Principal Investigator can request an extension of time to respond.

## CHAPTER 7 – IRB Submission Components

*This chapter contains information about the required components for submissions to the IRB and the various types of study submissions.*

### What Is the SpartaIRB System?

All IRB submissions (e.g., continuing reviews, modifications, continuing reviews with modifications, new studies, and reportable new information submissions) are to be created and submitted to the CWRU IRB via the SpartaIRB system (<https://spartaairb.case.edu>). The SpartaIRB Library contains various templates and forms. If there are any questions about which template is appropriate, please contact the CWRU IRB office at [cwru-irb@case.edu](mailto:cwru-irb@case.edu)

### Who Should be Added to the Study Team Member Table on the SpartaIRB SmartForm?

The CWRU IRB requires real time review of the personnel table. All individuals engaged in the research should be listed on the personnel table in the IRB submission. Individuals listed on the personnel table must have up-to-date training as required, and appropriate certifications. It is the PI's responsibility to determine whether individuals meet criteria to be engaged in research and should use the following guidelines to make that determination.

Individuals are generally considered to be NOT engaged in research when all of the following are true:

- The services performed do not merit professional recognition or publication privileges;
- The services performed are typically performed by those institutions for non-research purposes; and
- The individual does not administer any study intervention being tested or evaluated under the protocol.

### What Are the Documents and Information Required for IRB Protocol Submissions?

All protocol submissions must meet the criteria required under federal regulations. The research protocol describes the study and is used by the IRB to assess the scientific and ethical merits of the proposed study and whether it meets these criteria. The submission of a new or continuing protocol or modification to a protocol for IRB review requires the submission of a completed application or modification form, all relevant consent/assent documents, and all other study documents via the SpartaIRB system.

The new protocol submission for IRB review requires the documents to be uploaded in the correct sections of the Basic Information page of the study's SmartForm via the SpartaIRB system:

- *Protocol Section*- Protocol Template that matches the type of research
- *Informed Consent Section*- All relevant consent/parental permission/assent documents
- *Recruitment Section*- Includes correspondences with the participants (e.g., phone scripts, email messages, and letters) and advertisements
- *Other Section*- Includes Letter of Cooperation, Contracts, and other documents not fitting in the other categories.



## What Information Should Be Included in the Protocol Template?

The protocol template should include the required information:

- Protocol title: **full name** of study, including any study title acronyms or short title in parentheses
- Justification/rationale/significance of the study
- Purpose, including specific aims and/or hypotheses
- Study design including population to be studied, recruitment procedures and available resources
  - Upload and attach all study documents connected to the protocol (i.e., letter(s) of cooperation, data collection documents, data use agreements, etc.)
  - Upload and attach all recruitment documents (i.e., scripts, flyers, postcards, emails, etc.)
- Plan for obtaining informed consent, parental permission, and/or assent
  - Upload and attach all consent, parental permission, and/or assent documents
- Risks and discomforts to participants and how they will be minimized
- Subject privacy and data confidentiality
- Data analysis plan
- Benefits to participants
- Costs to the subject
- Payment to the participants (include both reimbursement and incentives)
- Alternative(s) to participation
- Provisions for participants from vulnerable populations
- References/Citations
- Plans, if any, for follow-up of the participants at the end of the protocol
- Funding source and grant identification number or contract (CON) ID

The IRB encourages the use of tables and flowcharts when they make the protocol easier to understand. The protocol should include a selective list of references that are related to the protocol. There is no limit to the number of pages, however the length of the protocol should be proportionate to the complexity of the study.

Ongoing study monitoring by the Principal Investigator is required for all studies to assure adherence to protocol and participant safety.

- For *not greater than minimal risk* studies, a plan that includes monitoring frequency and details of active oversight is expected.
- *Greater than minimal risk studies, including complex or multi-site studies, FDA-regulated studies including an IDE or IND, blinded or masked treatments, and those including vulnerable populations* are expected to include a DSMB (Data and Safety Monitoring Board) whose composition and schedule of meeting and reporting are delineated.
- *Greater than minimal risk studies of lower overall risk*, for example with a single site, a single intervention or bundle of interventions of lesser risk, or including washout, delay or placebo, are expected to have a SMC (Study Monitoring Committee) or an Independent or Safety Medical Monitor whose name(s), credentials and planned details of oversight are provided.

In all cases, monitors should be independent of the study, should have no real or apparent conflict of interest, and should not report to or be supervised by the Principal Investigator.



In general, the Medical Monitor has the responsibility to review and evaluate information relevant to safety during the conduct of the trial. They serve as an individual who is medically qualified to independently review the safety of the trial and have responsibilities including:

- Review protocol halting rules
- Advise protocol team on safety oversight
- Evaluate adverse events/SAEs and review safety reports
- Review deviations that affects the safety, rights, and welfare of the participant

## What Are the Detailed Requirements to Include in the IRB Protocol?

### *Purpose, Including Specific Aims and/or Hypotheses*

State clearly what is hoped to be learned from the research. The purpose should be written at a level that can be understood by individuals with a general medical background.

### *Background and Significance*

Discuss the relationship of the research to previous studies in the field and include pertinent references. Describe relevant experimental or clinical findings which led to the plan for the project. This must be succinct and comprehensible without reference to other material. For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternative modes of therapy. A few pertinent references should be cited, however exhaustive literature reviews are not necessary. If earlier studies have produced conflicting evidence, it is necessary to cite these studies and explain the rationale for the study design that was chosen.

The significance of the study for both the individuals participating and the advancement of knowledge should be stated. How significant is the new knowledge being sought in relation to the potential risks in carrying out the research?

### *Research Plan*

Inform the IRB of the specific nature of the procedures to be carried out on human participants in sufficient detail to permit evaluation of the risks. This section should also provide information that will allow the IRB to confirm the claim that methods employed will enable the investigator to evaluate the hypothesis posed and to collect valid data.

#### **a. Study Population**

Protocols must be precise as well as concise in defining a study population and how the population will be contacted. Describe recruitment procedures, including how it will be ensured that subject selection is equitable and that all relevant demographic groups will have access to study participation. Part of subject selection includes ensuring that no person is unduly denied access to research from which they could potentially benefit, without good reason (The Belmont Report, ethical principle of Justice). For example: to exclude non-English speaking individuals purely because it is inconvenient to have the consent form translated into an understandable language, or because the research staff does not speak the language, is not an acceptable reason for their exclusion. The IRB would determine this to be unfair and an injustice to those individuals.



In describing the equitable selection of participants, please ensure information is provided to justify the defined population(s) with regards to the following:

- The purposes of the research
- The setting in which the research would be conducted
- Whether prospective participants would be vulnerable to coercion or undue influence
- The inclusion/exclusion criteria
- Subject recruitment and enrollment procedures
- The amount and timing of payments to participants

**Subject Privacy:** Describe how you will protect the privacy of participants (i.e., what you will do to maintain an individual's interest in being left alone and being treated in a way that is comfortable to the individual). Describe the procedures for identification of possible participants and recruitment procedures.

**Inclusion and Exclusion:** The inclusion and exclusion criteria for both targeted participants and, if appropriate, control participants should be specifically stated. Assurance is required that there will be equitable selection of participants. Limited participation or exclusion of populations (e.g., minorities or women) must be justified.

Patients identified from medical records must not be contacted without permission from the responsible health care provider. The lack of a response from the responsible institution cannot be construed as approval to contact the patient.

If patients whose care is the responsibility of departments or special care areas other than that of the responsible investigator are to be involved, that department must provide information that will allow the IRB to confirm the claim that methods employed will enable the investigator to evaluate the hypothesis posed and to collect valid data.

If children are included as research participants the investigator must provide an assessment of the level of pediatric risk involved in the research. The final determination of risk level is made by the IRB.

**b. *Study Design***

Provide a description of the overall study design, including any procedures for randomization and/or blinding.

**c. *Assessment of Resources***

Investigators must include information in the protocol to ensure:

- Access to a population that would allow recruitment of the required number of participants
- Sufficient time to conduct and complete the research
- Adequate facilities (i.e., private room for consent and interviews)
- A process to ensure that persons assisting with the research were adequately informed about the protocol and their research-related duties and functions (i.e., verification of CREC certification)
- Availability of medical or psychological services that participants might require as a consequence of the research, if applicable



***d. Study Procedures***

All specific procedures to be performed on human participants for purposes of research should be detailed. It is important to distinguish between usual program implementation and/or class work and any experimental procedures. Include a description of the intended procedures as they directly affect the participants. There need not be a detailed account of techniques that do not directly affect the human subject (e.g., details of laboratory methodology). Do include:

- The number and estimated length of study visits/interactions
- The length of time for various procedures and frequency of repetition
- Any procedural aspects that may cause discomfort or inconvenience
- Plans for post-study follow-up, if applicable

A general time schedule for various procedures should be provided, showing what a subject might expect regarding how long each aspect of the study will take; the frequency and timing of ancillary procedures; and the duration of discomfort. It would be helpful to present complicated studies with a simple flow chart to enhance the narrative description. The location of the study must be indicated.

***e. Funding Source***

Funding source must be identified in the study protocol and the grant identification number or contract ID added to the SpartaIRB Smartform.

***f. Electronic Record System Use***

If study procedures require the use of electronic documentation systems (i.e., electronic medical records, learning management systems, electronic data sets), the following information must be included in the research protocol:

- Justification for use of the system and why this information cannot be obtained in another manner;
- What information will be collected from the system and the specific process for collection;
- How that information will be protected and secured including how long access to that information will be necessary through the electronic system;
- Who will perform the data collection; and
- Permission from the data source in the form of a letter of cooperation, IRB approval, and/or data use agreement.

***Risks and Discomforts and How They will be Minimized***

Potential research risks include more than physical harm: risks may also include emotional or psychological harm, social risk of stigmatization, and economic or legal risk. There should be a description of all known or potential risks, discomforts, or inconveniences to the subject. This should include the investigator's explanation of how they concluded that the risks to participants are reasonable in relation to anticipated benefits to participants, if any, and the importance of the knowledge that may reasonably be expected to result from the research. The description of risks may be extensive or may be brief, depending on the protocol. Risks related to the research need to be distinguished from risks that are part of standard program implementation or standard of care.

Participants should be told what will be done to minimize risks and which risks, if any, might be irreversible. Describe the procedures for protecting against or minimizing potential risks and assess their



likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.

There are specific risks that may be present when genetic information is part of a protocol. The magnitude of the risks and a description of the risks should be given in both the protocol and the consent form. These risks may include:

- Future problems with access to or retention of benefits or entitlements (e.g., health insurance, life or disability insurance, educational opportunities, employment, etc.).
- Stigmatization: negative views of others, about the participant, within or without the participant's family; the possibility of altered family relationships and interactions.
- Psychological responses to information: altered self-concept; possible feelings of depression, guilt, anger, etc.
- Detection of previously unknown biological relationships within a family: paternity, maternity, and adoption.

### *Compensation for Injuries*

For any research involving more than minimal risk, federal regulations require an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained. The Principal Investigator may need to distinguish between treatments for injuries related to the investigational intervention versus treatments for routine program implementation. If a study entails minimal risk and if, in the opinion of the investigator, there is the potential for physical injury, an “in case of injury” section should be incorporated into the protocol and consent form.

“In case of injury” provisions should include:

- Where and from whom medical therapy may be obtained.
- What therapy will consist of and its duration.
- Who will pay for the therapy?
- Whom to contact in case of injury.
- What happens after the study ends or if the subject is dropped from the study?

The source of funds, if any, to cover the costs of medical therapy for injuries should be specified. If none is available, it is important that the subject understands what may be billed to them or to a third-party payer. This includes routine medical care that is normally billed to the subject even when it is performed in conjunction with a research study.

### *Benefits to Participants*

Describe the potential benefits to the individual participants enrolled in the study. If there are no direct benefits, indicate there are none. Reimbursement or compensation is never a benefit. The potential benefits which may result for other individuals, general knowledge, etc., should also be discussed. For studies with greater than minimal risk, discuss why the risks to participants are reasonable in relation to the anticipated benefits to participants and in relation to the importance of the knowledge that may reasonably be expected to result.

### *Costs to Participants*

Investigators must address any extra costs incurred because of the research project. If costs due to research are to be incurred by the subject, such costs must be stated on the consent form. Describe and justify any costs that the subject will incur as a result of participation; normally, participants should not have to pay for research procedures that do not provide some direct benefit.

### *Alternative(s) To Participation*

Discuss the alternatives to participating in the study. Are some or all of the study components available without participating in the study? Can a former participant or someone who refuses to participate in the study remain in the program or class?

### *Payment to the Participants (Recruitment Inducements/Reimbursement)*

Describe any material inducements that will be offered to participants in return for their participation, e.g., direct payment, food, test outcomes, etc. Discuss both reimbursement for expenses (e.g., parking and meals) and payments for time, effort, inconvenience and discomfort. Describe the schedule of payment to participants based on their complete or partial participation (prorating). Identify whether early withdrawal from the study will result in a reduced payment or whether it makes a difference if it is the participant or the investigator who decides to terminate the subject's participation.

### *Plan for Obtaining Informed Consent (Informed Consent Process)*

Describe all plans for obtaining consent and/or assent, justifications for requesting consent waivers and/or process alterations, and processes for non-English speakers and other vulnerable populations (e.g., CWRU employees, cognitively impaired individuals, etc.).

#### **a. Description of the Informed Consent Process**

The protocol must include a description of the informed consent process. Please consider the following points:

- The timing/waiting periods for participants to ensure that they are allowed adequate time to make an informed decision and to minimize the possibility of coercion or undue influence. Sufficient time must also be allowed for the subject to review and consider participating with the assistance of family members, research partners or representatives if necessary. Other items to consider regarding time/waiting periods are: Is the potential subject given a copy of the consent form to read prior to the discussion of the study? Is the consent form presented in person or mailed to participants (where they can review it in the privacy of their own home)? How much time elapses between the presentation of the study and informed consent form and the actual signing of the form?
- The steps taken to minimize the possibility of coercion or undue influence
- The language used by those obtaining consent
- The language understood by the prospective subject or the representative
- Who will be involved in obtaining consent?
- Who will be approached for consent/assent/permission (parental or guardian)?





***b. Comprehension of Informed Consent***

In order for the IRB to evaluate issues of comprehension, the protocol needs to describe the steps taken to ensure that participants or their legal representative, and those who are involved in obtaining consent, understand the research. Once a potential participant is identified, what process is followed to inform the subject of the study prior to obtaining a signature on the informed consent form? Please consider the following points:

- Who introduces the study to the potential participant?
- Who reviews with the participant the informed consent document in depth?
- Do you require the potential participant to have another person present during the presentation of the study?
- Who answers the questions presented by the potential participant and/or family?
- What method is used to determine if the potential subject fully understands the study, what is required from them, risk and benefits, and their rights as a subject?
- Is the Principal Investigator usually present during the presentation of the informed consent?

Although written consent forms are generally required, in studies that present no more than minimal risk of harm to participants and involve no procedures for which written consent is normally required, oral consent may be approved. Written consent may also be waived if the consent form is the only record linking the subject to research involving sensitive information and the primary risk of the research would be breach of confidentiality.

If the investigator believes that oral consent is appropriate, the request for waiver of written documentation of consent must be justified in the protocol. If the IRB approves the waiver of written consent, i.e., verbal or oral consent, an information sheet or a document that addresses the required elements of informed consent, may be required for participants.

***c. Provisions for Participants from Vulnerable Populations***

Address whether some or all participants to be recruited will be vulnerable to coercion or undue influence. If they are, describe the additional protections provided to these participants to protect their rights and welfare. Under The Belmont Report, the ethical principle of Beneficence requires that risks to participants are outweighed by the sum of both the anticipated benefit to the subject and, if any, the anticipated benefit to society (i.e., knowledge to be gained). In reviewing research involving vulnerable participants, the IRB is required to determine whether the presented risks are fully justified, and the appropriateness of their inclusion has been demonstrated. For example, if participants who may not be competent to give consent are to be included, a description of how competency will be assessed needs to be included. Vulnerable Populations include:

- Cognitively-/Decisionally-Impaired Persons (including dementia-affected people & the mentally ill)
- Minors
- Non-English-Speaking populations
- Physically Challenged Persons
- Pregnant Women, Fetuses and Neonates
- Prisoners
- University Employees
- University Students
- Wards of the State



**d. *Subject Privacy and Data Confidentiality***

*Note: Confidentiality concerns data and Privacy concerns people*

Describe the provisions to protect a subject's privacy and the confidentiality of their data in connection with their participation in the research study. Ensure that you include a description of:

- How identifiable information will be accessed.
- How the information obtained will remain confidential; how will you store and secure data?
- Who will have access to said data.
- What will happen with/to identifiable research data once the study is completed.
- If applicable, that information will be disclosed only with the subject's permission or as required by U.S. or Ohio law. Examples of information that are legally or ethically required to be disclosed include abuse of a child or elderly person, and certain reportable diseases.

**Privacy of Participants**

Privacy refers to a person's desire to control access of themselves to others. Describe how you will protect the privacy of participants (i.e., what you will do to maintain an individual's interest in being left alone and being treated in a way that is comfortable to the individual). Describe specifically the procedures for identifying participants; how you will gather information from or about them; and how any invasion of privacy will be minimized. Please also consider the location where the information is to be gathered and whether the participants will be comfortable in the proposed research setting. *EXAMPLES: People may be uncomfortable answering questions about their employer in an open cubicle, so investigators may arrange for a more private interview location; people may not want to be seen in a place that might be stigmatizing to them, such as a pregnancy counseling center, so investigators may arrange for questionnaires to be mailed to participants.*

**Confidentiality of Data**

Confidentiality refers to keeping data secret/protected within a small group of research staff; confidential data are not intended to be shared/disclosed publicly. Describe how research data will be stored and secured to ensure confidentiality. If data will be shared with other investigators, explain why this is necessary and, if relevant, justify releasing data with identifiers that would permit the recipient investigator to know or infer the identity of the subject [[45 CFR 46.111\(a\)\(7\)](#)]. If highly sensitive information is to be gathered, such as information that would put the subject at risk of criminal or civil liability, either provide a Certificate of Confidentiality or explain why one was not requested. If audio or video tapes are made for research purposes describe how they will be kept secure and when they will be destroyed.

Further describe the disposition of information obtained during a study. When a study is of a diagnostic or therapeutic modality, information is very often entered in the subject's medical record, discussed with the subject, and transmitted to anyone else whom the subject designates.

When participants will be tested for reportable diseases, such as HIV or hepatitis, the protocol must clearly reflect these exceptions to confidentiality. Limits on confidentiality, such as inspection of records by the IRB, should also be explained.

*Data Analysis Plan*

Summarize the statistical/analytical methods to be used.

### *Plans for Participants at the End of the Protocol*

Are there any post-research follow-up contacts? Do you want to hold on to contact information for future studies? If so, you must include this request in the consent process and documents.

### *When the Investigator is the Lead Investigator of a Multi-site Study*

The IRB evaluates whether the management of information that is relevant to the protection of participants is adequate.

When the investigator is the lead investigator of a multi-site study, applications include information about the management of information that is relevant to the protection of participants, such as:

- Unanticipated problems involving risks to participants or others
- Interim results
- Protocol modifications

### *Regarding Protocols with Approval of IRBs from Other Institutions*

On occasion, faculty and student researchers who are working primarily at institutions other than CWRU may have protocols approved by their respective institutional review boards and these investigators want to collaborate with CWRU faculty member(s). If the collaborating researchers would like to have their institutions enter into a Reliance Review Agreement (RRA) for one institution to rely on the other Institution's IRB, the RRA Process must be followed. The CWRU faculty member should contact the Executive Director for the Human Research Protection Program (kav6@case.edu or 216-368-0134). Otherwise, if the study is not federally funded, then each faculty member can submit a protocol submission, which describes their engagement in human participants research activities and the overall collaboration between the researchers, to their own IRB.

## Where Are the Informed Consent/Assent Forms Located?

If consent will be obtained, the use of the appropriate consent template is required. Consent templates are located in the Templates Tab of the SpartaIRB Library and can be tailored to the needs of the study. The PI and study team members should make sure that the consent template designated for the CWRU IRB is used (**not** the UH IRB).

- All consent documents must contain all of the required and additional appropriate elements of informed consent disclosure.
  - The template heading, title of protocol, and page numbers must appear on all pages. This ensures that auditors can verify all pages are in order and from the same document.
  - It is recommended that the date of revisions to the consent documents are noted to ensure that the stamped, most recent version approved by the IRB is being used.
  - Additional information on consent form requirements can be found in Chapter 10- General Requirements for Informed Consent.
  - In a new study submission, the consent document is to be uploaded to the Consent Forms Section of the Local Site Documents page in the study's SmartForm.
- When making any changes to the consent with a modification to the study, ensure utilization of the "Update" button found next to the original consent in the study's SmartForm to stack revisions on

top of older versions. To clarify, each item under a section is seen as its own entity so if documents are not stacked appropriately, it will appear as if the study has more than one consent form.

**For more information, see Chapter 10 – General Requirements for Informed Consent**

## What Are Study Modifications?

The CWRU IRB reviews and approves all modifications (i.e., revisions, amendments, additions and deletions) to an IRB-approved research protocol.

The IRB will review all proposed changes to approved research to determine whether the change(s) are consistent with ensuring the participants' continued welfare. The IRB guidance states that any revisions, changes, additions or deletions in procedures, alterations of risk compared to the original protocol, or changes in subject population must be reviewed and approved by the IRB via expedited or full review prior to implementing the proposed change(s) ([§46.108](#), [§46.110](#)). Major changes in study design or the application of a study to a very different population usually require a new protocol.

### *Examples of Modifications*

- Revisions to a protocol including:
  - Sponsor amendments
  - Administrative or editorial changes or addenda
  - Changes or additions to eligibility criteria
  - Changes or additions to a procedure
  - Changes or additions to a study instrument
  - Addition or removal of study site(s)
- Changes to enrollment number
- Revisions to consent or assent form
- Changes to study investigator
- Changes in study personnel
- Changes in recruitment practices including:
  - Change in research population
  - Letters to potential participants
  - Notifications and/or letters to research participants
  - Advertising materials- media/internet, press releases, flyers, etc.
  - Recruitment materials

## What Are the Requirements for a Modification Submission?

Investigators who wish to make alterations to an IRB-approved protocol must submit a modification form to the IRB via the SpartaIRB system, prior to initiation of the alteration. Therefore, research must continue to be conducted without inclusion of the modification(s) until IRB approval is received. The only exception is a change necessary to eliminate apparent immediate hazards to the research participants or to a participant's safety. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the participant(s) continued welfare. The form must be completed to include a written description of the proposed change(s) and the reason for the change(s). The modification form must include all new and/or revised study documents that would be affected by the proposed change(s) (i.e., consent form,



questionnaires, scripts, etc.). If the proposed change(s) affects the protocol, the modification form must include an uploaded revised version.

The IRB will reassess the balance of risks to benefits in light of the proposed change and may require the research to be modified or terminated. Only those individuals noted as Principal Investigator or Co-Investigator have the authority to submit change requests on their protocol.

The investigator must determine if the modification significantly alters the basic design of the study or changes the risk/benefit ratio for participants. Modifications that alter the research method design that increases the risk/benefit ratio will be reviewed by the convened IRB. If the risk/benefit ratio has changed, the investigator must also determine whether participants currently and/or previously enrolled on the study will be re-consented. The investigator will need to amend the currently approved informed consent document(s) to reflect the change. In addition, when reviewing information relating to protocol changes, the IRB is required to assess whether the information should be provided to the participants, when such information might affect their willingness to continue to take part in the research.

Approval from the Department Review Committee and/or Department Chair or Dean is required if the modification significantly alters the design of the study, impacts the risk/benefit ratio, or if requested by the IRB.

When modifications include changes to study documents, utilize the “Update” button found next to the original document in the study’s SmartForm to stack revisions on top of older versions.

In order to add research sites to previously approved protocols, a modification must be submitted to the CWRU IRB for review and approval. The modification must include site-specific information, including but not limited to consent forms, conflict of interests management plans, etc., to be used at the relying site. When no significant changes to study procedures are requested / included by the relying site, this may be considered a minor modification that can be reviewed via expedited review.

## When Is a Continuing Review Required Under the Revised Common Rule (2018 Requirements)?

The Revised Common Rule modifies when continuing review is required. Unless the CWRU IRB determines otherwise, continuing review of research is not required for research subject to the revised Common Rule in the following circumstances:

1. Research eligible for expedited review in accordance with §46.110
2. Research reviewed by the IRB in accordance with limited IRB review
3. Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
  - a. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
  - b. Accessing follow-up clinical data from procedures that participants would undergo as part of clinical care

The CWRU IRB may determine that continuing review is required for any research protocol that falls within the above criteria. The CWRU IRB shall take the following factors into consideration to determine if continuing review is required:



1. Required by other applicable regulations (e.g., FDA);
2. The research involves topics, procedures, or data that may be considered sensitive or controversial;
3. The research involves particularly vulnerable participants or circumstances that increase participants' vulnerability;
4. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
5. An investigator has a history of noncompliance.

When the CWRU IRB determines that a continuing review is required for such research, it will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

Studies with no expiration date may periodically be contacted by the IRB with a check-in notice to confirm that the study is still open and to remind PIs of their responsibilities. In some situations, the IRB will attempt additional correspondence if the study team does not respond. In cases where the IRB receives no response from the study team after multiple attempts, the study could be closed.

The Principal Investigator/PI Proxy will be required to update the IRB on the study with an annual check-in and verify that all study personnel are CREC certified and have a COI disclosure form on file.

## What Happens to Research Protocols That Are Initially or Previously Reviewed by a Convened Meeting?

All IRB members will have access to all the study documentation, including: the continuing review application, the current informed consent document, any newly proposed consent documents and revised research plans, the complete protocol including any protocol modifications previously approved by the IRB, and a status report on the progress of the research.

Access to additional information in the IRB protocol file is available in the SpartaIRB electronic IRB system. An IRB administrator or designee will make these items available for review upon their request.

The Board may require certain projects, as determined by an evaluation of the risk-benefit ratio, to be reviewed more frequently than yearly. For example, this can be either after a fixed period of time such as at six months or after a certain number of participants have been enrolled or studied (an expiration date will also be set). The expiration date for an IRB approved study is clearly indicated on the IRB approval letter and is the last day that the study is approved.

The minutes of the IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing continuing review. The rationale for any requested revisions must be documented. The minutes of IRB meetings will reflect the IRB's determination regarding which protocols require continuing review more often than annually. The minutes will reflect any change in the level of risk (e.g., minimal or greater than minimal). All requested changes and/or requests for additional information will be communicated to the Principal Investigator.



## What Happens to Research Protocols That Were Initially or Previously Reviewed by the Expedited Review Process?

Research protocols that were initially reviewed using the expedited review process may receive continuing review on an expedited basis, unless the previously met criteria in [45 CFR 46.110](#) has changed. The expedited review procedure is conducted by the IRB Chair, Vice Chair or an experienced member of the IRB designated by the IRB office, and as needed with the assistance of the Executive Director for HRPP. When reviewing research using the expedited procedure, the reviewers utilize the same information provided at Full Board review, as outlined above.

## What Happens to Protocols That Originally Underwent Full Board Review and Now Qualify for Expedited Continuing Review?

Research protocols initially reviewed by a convened IRB but meeting one of the following criteria may also qualify for expedited review at continuing review:

- **Subject Follow-up Only** The research is permanently closed to enrollment of new participants, all participants have completed all research-related interventions, and the research remains active only for long-term follow-up of participants.
- **Delayed Start** When no participants have been enrolled at CWRU and no additional risks have been identified.
- **Data Analysis Only** The remaining research activities are limited to data analysis.
- **Prior Board Approval for Expedited Continuing Review** Studies subject to the Pre-2018 Common rule that met the criteria for expedited review but, by the option of the IRB Chair, were initially reviewed at a Board meeting or are minimal risk but not clearly in one of the approvable expedited review categories can receive expedited continuing review if expedited continuing review was approved by the Board at the time of the convened Board review and documented in the minutes. Studies initially reviewed by the IRB under the new common rule that are determined to be not greater than minimal risk will typically not be required to submit continuing reviews. However, whether that continuing review can be approved through expedited review will be determined by the Board at the time of initial approval or subsequent continuing review and documented in the minutes.

## When Is a Continuing Review of a Protocol Required?

The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) have specific regulations regarding IRB continuing review of ongoing research, to ensure that the rights and welfare of human participants are protected.

The aims of continuing review are to reappraise the research to ensure:

- The risk/benefit ratio is still acceptable.
- The measures taken to safeguard participants are adequate.
- The approved protocol is being followed.
- The protocol reflects changes in the regulations for human participants' research that have been implemented since the last approval.
- To review the progress of the protocol since last review and the plans for the future based on the progress to date.



- Review adverse events, untoward reactions, or unanticipated problems that occurred since the last review.
- Evaluation of new significant findings that might relate to the participant's willingness to continue and which should be provided to participants.
- All local requirements are still being met, including verification of current study personnel certifications.

Although continuing reviews are usually assigned an expiration date of one year, the IRB may require certain projects, as determined by an evaluation of the risk-benefit ratio, to be reviewed more frequently than yearly. This can be either after a fixed period of time (such as at six months) or after a certain number of participants have been enrolled.

## What Happens With Protocols That Were Approved Under the Pre-2018 Common Rule and Cannot Be Moved to the Revised Common Rule?

The IRB may also grant an extended period of approval of up to 3 years for research that is not federally funded, not greater than minimal risk, and not subject to COI review.

Research approved by the IRB may only continue for the approved duration set by the IRB. Additionally, continuing review must occur until data collection and data analysis on identifiable data are complete. However, data analysis (not data collection) can continue after study termination if the data are de-identified.

Research approved by the IRB may only continue for the approved duration set by the IRB.

The Continuing Review submission must include information about:

- Progress of the study
- Number and type of participants enrolled since the last approval
- Summary of protocol events and deviations (if any)
- Report of subject complaints (if any), and
- Review of any significant, relevant literature published since the last approval.
- If any changes are proposed since the last IRB review:
  - The Modification should be described
  - Revised documents should be submitted

All significant new findings that arise from the continuing review process and relates to a participant's willingness to continue participation must be provided to participant by the Principal Investigator.

## How Long Is a Protocol Required to go through the Continuing Review Cycle?

Continuing review must occur until data collection and data analysis on identifiable data are complete. However, data analysis (*not* data collection) can continue after study termination if the data are de-identified.

## What Information Is Required to be Included in the Continuing Review Submission Sent to the IRB in the SpartaIRB System?

The Continuing Review Form in the SpartaIRB system must include general information about the study progress. All applicable study milestones listed on the SmartForm should be addressed. Additionally, the continuing review must be complete, informative, succinct, and must address the following:

- Indication of enrollment activity
- Total number of participants
- Total Number and types of participants enrolled since the last review
  - Which must not exceed the IRB approved enrollment numbers
  - Enrolling over the number listed on the IRB forms is not permitted and could be considered non-compliance
- Number of participants to be enrolled in the upcoming year
- Number of participants that have withdrawn from the study and the reason for their withdrawal
- Summary since the last IRB continuing review of all adverse events; unanticipated problems involving risks to participants or others; and protocol deviations
- For adverse events, the description should also include:
  - Seriousness of the events, i.e., death, serious, or non-serious
  - Whether the events were expected or unexpected
  - Whether the events were study related, possibly study related, not study related, or unknown relation to the study
  - Whether the frequency, severity or specificity of adverse events has changed.
  - For external adverse events, a statement regarding whether the events affect the conduct of the research (e.g. risks; benefits; alternatives)
- Summary of subject complaints
- Problems associated with the recruitment of participants
- Summary of the study findings, including results and publications; and an assessment as to whether the risks and benefits of the research have changed
- Any relevant publications/data that would affect the risk/benefit ratio
- Change in investigator conflict of interests; including new financial interests
- Description of approved modifications since the last review
- Description of the plans for the upcoming year

The PI and study team must also confirm that:

- In the opinion of the PI, the risks and potential benefits are unchanged
- All modifications to the protocol have been submitted to the IRB
- All problems that require prompt reporting to the IRB have been submitted

### ***Informed Consent Documents***

The current approved informed consent documents, along with any revisions submitted at the time of continuing review, will be reviewed by the IRB to ensure that the information is still accurate and complete, and that participants are fully informed of the risk and benefits associated with the research. Any significant new findings that arise from the continuing review process and relates to or may affect the participants' willingness to continue to participate must be disclosed in an updated informed consent document. The IRB may require the PI to provide this information to participants who have completed the study.



***Modifications to Protocol Submitted at the Time of Continuing Review***

Modifications or revisions to a research protocol, including informed consent documents, may be submitted at the time of continuing review. It is necessary for all appropriate documentation addressing the modification to accompany the submission. The IRB **must** review and approve a modification prior to its implementation.

## What Are the Principal Investigator’s Responsibility to Prevent a Lapse in their Protocol?

The expiration date (if any) for an IRB approved study is clearly indicated on the IRB approval or initial approval letter and is the last day that the study has IRB approval. Additionally, the date by which a protocol must receive its continuing review is listed on the approval letter and indicates the date that the protocol is approved through.

The Federal Regulations and the CWRU IRB do not allow for the conduct of research beyond the protocol approval end date. The investigator is responsible for ensuring that the research is submitted to the IRB for continuing review in an appropriate time frame, in order to avoid a lapse of IRB approval.

The Principal Investigator is responsible for ensuring that the research is submitted to the IRB for continuing review in an appropriate time frame, in order to avoid a lapse of IRB approval.

- The CWRU IRB recommends that a Continuing Review is submitted at least 6 weeks prior to the expiration of the study.
- If the continuing review involves modifications to previously approved research, it is usually best to submit those modifications as a combined Modification and Continuing Review in the SpartaIRB system.

The SpartaIRB system will indicate when a protocol is ready to expire and will automatically send courtesy notices at 90-day, 60-day, and 30-day intervals alerting the investigator to submit a continuing review. If no continuing review is received before the approval end date and the protocol expires, the SpartaIRB will send notice to investigators on the protocol’s expiration date that their protocol has lapsed.

## What Steps Are Required to Close a Multi-Site Study When Each Institution Has Their Own IRB Approval?

If the research is being conducted at multiple institutions, and the CWRU IRB approved only the research being conducted by CWRU investigators, then a protocol can be closed at CWRU when all Human Research activity at CWRU has been completed. For example, researchers from CWRU collect data from a survey sent out to CWRU students which will be analyzed in combination with student survey data collected by investigators from another institution. Once the data collected at CWRU has been sent to the collaborating institution for analysis, and no additional Human Research activities will be conducted at CWRU, then the researchers at CWRU may close the protocol.

## What Steps Are Required to Close a Multi-Site Study That Involves a Single IRB Approval?

When CWRU is relying on another IRB (External IRB), the protocol site record at CWRU IRB may be closed when Human Research activities conducted by CWRU researchers are completed. A modification should be submitted in the SpartaIRB system indicating the intent to close the site record. The investigator will need to notify the PI at the reviewing institution that the site record at CWRU will be closed.

When the CWRU IRB is the IRB of record, the CWRU protocol may only be closed once all sites, including CWRU, are no longer engaged in Human Research activities. The CWRU PI should communicate to all co-investigators at institutions with reliance agreements with CWRU when the protocol will be closed.

## What Happens If a Protocol Submission Lapses?

The SpartaIRB system will send an Administrative Hold/Protocol Expiration notice to inform the investigator that all research activities must cease and, if federally funded, the Office of Sponsored Projects will be notified and asked to cease all federal funding activities (i.e., reimbursement) related to the study. Further, investigators must inform the IRB if any research activities have occurred after the expiration date (a non-compliance issue, which will be processed as described in **Chapter 24 – Non-Compliance Involving Human Research**).

If a protocol has lapsed, the investigator has thirty (30) days from the protocol expiration date to submit a continuing review form. Within the Administrative Hold period, no research activity, including data analysis may occur. Research activities include but are not limited to the following:

- Screening
- Recruitment
- Enrollment
- Consent
- Advertisement
- Study interventions and subject interactions (i.e. any involvement of current participants including the scheduling of study visits) -AND-
- Analysis or Collection of identifiable data; this also includes looking at new participants information

If a continuing review submission is not received for review within the 30-day Administrative Hold period, the IRB will administratively close the protocol. A notification will be sent in the SpartaIRB system regarding Administrative Closure.

If an investigator wishes to resume their research protocol, the investigator must submit a termination form to properly close out the terminated protocol and submit a new protocol application to resume the research.

## What Are Circumstances When the IRB Would Allow Continuation of Study Interventions During the Lapse in the Protocol?

The IRB has the authority to allow the continued participation of participants in research for which IRB approval has lapsed while the continuing review process occurs, **only** if there are overriding safety concerns or ethical issues that indicate it is in the best interest of the participants to continue, for example when the research interventions have the prospect of direct benefit to participants or when withholding the study interventions poses an increased risk to participants. In such cases, the study will be closed to new enrollment and all data analysis must stop until the IRB completes the review process.

If an investigator decides that immediately stopping all or some of the research activities would not be in a participant's best interest, the investigator must inform the IRB via the SpartaIRB system.

- This formal request must be made as a Modification and must include the rationale and justification as to why the research activities should be allowed to continue.
- It should also include a confidential list of the research participants (identified by study number or initials only) for whom suspension of the research would potentially increase risk or deny benefits.
- The determination by the IRB may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB.
- Furthermore, this determination may be made for all enrolled participants as a group or for each individual participant.
- If the investigator or IRB determines that it is not in the best interests of already enrolled participants to continue to participate, investigators must stop all human research activities ([45 CFR 46.109\(a\) and \(e\)](#)), including:
  - Intervening or interacting with participants and
  - Obtaining or analyzing identifiable private information about human participants

The IRB will acknowledge the closure of a study by sending a letter via the SpartaIRB system. After a protocol has been closed the IRB does not accept reports of adverse events unless they impact the rights and welfare of participants enrolled or the integrity of the data. The investigator should keep all non-reported adverse events on file for review by regulatory agencies as required.

After a study has been permanently closed, signed consent forms should be available for IRB inspection for three years. In the event the Principal Investigator departs from CWRU, copies of signed consent forms should be given to a CWRU co-investigator or archived in accordance with the [Custody of Research Policy](#).

Closures/Terminations are included in the Notice of Committee Report to the IRB and those reports will be maintained by the CWRU IRB office.

If the investigator continues to conduct the research after the study has expired (without prior approval from the IRB that it is in the best interest of the current participants to continue activity), this becomes an issue of non-compliance and will be processed as described in the CWRU IRB Member Manual and is reportable to the IRB via the SpartaIRB system. The matter may also be reportable to the CWRU Compliance Officer and to applicable regulatory or funding agencies.



## What Is the Annual Check-In For Studies With No Expiration Date?

Under the Revised Common Rule, certain studies can now be approved without an expiration date. However, the CWRU IRB and HRPP are still required to maintain oversight of all open research. Thus, the CWRU requires a study closure form when the research is complete. Until a closure form has been processed by the IRB, notifications will go out to the Principal Investigator, PI Proxy, and Study Contact, if applicable, on a yearly basis with an Annual Check-in request.

The Principal Investigator/PI Proxy will be required to respond to these Annual Check-in notices with a brief communication of study status (e.g., study is ongoing and should remain open), verify that all study personnel are CREC certified/have COI disclosure forms on file, and report any minor protocol deviations, adverse events, participant complaints, or unanticipated problems that did not meet the time-specific RNI reporting requirements (see CHAPTER 27 – Reportable New Information. If the study has been completed, this should be communicated in the Annual Check-in, and a Study Closure form should be submitted.

**Study teams that do not respond to the Annual Check-in will be referred to HRPP Office to investigate study status.** Failure to respond regarding these study status inquiries may result in a QIP Review (see CHAPTER 25 – Quality Improvement Program (QIP) Reviews).

Please note that while a formal Continuing Review is not required by the updated regulations for these studies, all research is still subject to, and must comply with, federal and local research regulations and policies, including random research compliance audits.

## When Can an Approved IRB Protocol be Closed?

Investigators are responsible for closing approved protocols when they no longer involve Human Research activities. A protocol no longer involves Human Research activities when all research-related interventions or interactions with human participants have been completed, and all data collection and analysis of **identifiable** private information/biospecimens described in the IRB approved protocol has been finished.

At the time of closure, investigators may keep the data collected, including identifiers, as long as the study team is no longer using or analyzing the data/specimens linked to identifiers. For example, if identifiable data or identifying links are being maintained so that participants can be contacted if necessary, but the data are no longer being analyzed, then the protocol can be closed. However, if analysis of a coded data set is ongoing, and the study team maintains a master list linking the identifiers to the data, this is considered Human Research and IRB approval must be maintained.

For protocols involving HIPAA Authorization obtained from study participants, permission to use the protected health information (PHI) may have been granted for an extended or indefinite period of time. However, this permission is intended for analysis of PHI when the protocol is open. Therefore, the protocol must remain open while using PHI.

Notification of protocol closure should be sent to the IRB office by completing the electronic Continuing Review/Study Closure Form in the SpartaIRB system. The IRB will acknowledge the closure of a protocol by sending a notification. After a protocol has been closed, only adverse events that impact the rights and welfare of previously enrolled participants or the integrity of the already collected data should be reported to the IRB using the Report New Information form in SpartaIRB.

When a protocol is closed, the only research activity that may occur is analysis of data with no link back to identifiers. Once the data are no longer identifiable, they can be retained indefinitely. To resume Human Research activities (i.e., secondary analysis on identifiable data/specimens), a new protocol must be submitted and approved by the IRB.

After a protocol has been closed, signed consent forms should be available for IRB inspection for a minimum of three years. If your research was supported by external funding, or was subject to HIPAA, FERPA, a Data Use Agreement, or other federal or state requirements (including FDA), please contact the IRB Office to help determine whether additional data retention requirements may apply. In the event the Principal Investigator departs from CWRU, original signed consent forms should be given to a CWRU co-investigator or archived in accordance with the CWRU Faculty Handbook.

## How Is a Study Closure Request Completed and Submitted to the IRB?

Complete the Continuing Review SmartForm in the SpartaIRB system and attach all requested documents. To request a study closure, select the first four research milestones under #2 in the SmartForm. Once completed, the PI or PI Proxy will need to click “Submit” to send the submission to the IRB. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Please be mindful that certain sponsors, including the NIH, might have additional record retention policies. If your Human Research is sponsored, contact the sponsor before disposing of Human Research records. After a protocol has been closed, the IRB does not accept further submissions unless they impact the rights and welfare of participants. The investigator should keep all non-reported adverse events on file for review by regulatory agencies.

After study closure the study no longer has IRB approval and all human subject research activity must cease. **Important:** Once a study closure has been submitted and processed by the IRB the study cannot be re-opened.

## How Long Should Records be Retained?

Regulations and study sponsors require investigators to retain research data not only while research is being conducted but also after the research is complete.

- Human Research records, including signed and dated consent documents for at least three years after completion of the research.
- Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for at least six years after completion of the research.
- See also [SOP HRP-072: IRB Records Retention](#) for more information.

Regulatory/Oversight	How Long to Retain Records
CWRU Data Retention & IRB Policy	3 years after last publication
Food and Drug Administration (FDA)	2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified

	<i>*Reference Chapter 29 for more FDA guidance</i>
Office for Human Research Protections (OHRP)	3 years after study closure
Health Insurance Portability Act (HIPAA)	Signed Authorizations (i.e., consent forms) for 6 years after study completion
Sponsor	Comply with any term for record retention detailed in the contract

## Other IRB Submissions

Please refer to **Chapter 27 – Reportable New Information** and **Chapter 28 – Reliant Review Agreements for Single IRB Review** for more information regarding additional IRB submission types and requirements.

## CHAPTER 8 – Required Reviews and Approvals

*This chapter includes information about required department approvals, as well as additional required reviews and approvals needed before submission.*

### What Is a Department Scientific Review of Protocols?

It is the policy of the CWRU IRB that each Department reviews all protocols prior to submission to the IRB. The review must address scientific merit, ethical issues, scholarly validity, and the availability of Departmental resources to carry out the research. Departmental review allows the Dean, Chair, or Vice President of the Department to be aware of Departmental research activities and provides information for allocation of Departmental resources.

The scholarly or scientific review of proposed research should address the following issues, as a minimum:

- Does the research use procedures consistent with sound research design?
- Is the research design sound enough to yield the expected knowledge?

Principal Investigators submitting new protocols to the IRB must submit to their Department for review and approval. Review by the Department applies to new protocols and modifications with major study design changes or changes that alter the level of risk to participants. The IRB will not review or approve any protocol that has not been reviewed and approved by the Department.

The scientific review is documented and communicated to the IRB through the sign-off process and attestation. If the IRB has questions regarding the scientific or scholarly merit, process, etc. these are referred back to the Reviewing Dean/Chair/Vice President for further input.

Additionally, for all protocols that will study proactive research activities related to any aspect of cancer, an application is required to be submitted to the CWRU Comprehensive Cancer Center's Protocol Review and Monitoring Committee (PRMC) <https://case.edu/cancer/research/clinical-research-office/prmc>

### What Are the Functions and Organization of a Department Scientific Review of Protocols?

The function of the department's research review is to:

- Review the scientific merit of a protocol
- Review the available resources (including qualified staff, appropriate population and adequate facilities) to carry out the proposed research within the department
- Determine if the PI and study team have appropriate expertise to conduct the study
- Review the proposed time to conduct and complete the research
- Review ethical concerns related to the study risk especially as it relates to the discipline represented by the department
- Review the protocol and consent form to ensure that the required elements are present before forwarding the protocol to the IRB for review
- Review amendments to approved protocols if the amendment adds significant risk to the participants or significantly alters the study design or procedures
- Serve as an educational resource for faculty and staff of the department on human subject protections



Each department's research review will:

- Ensure timely and prompt review of new protocols submitted for review
- Designate support staff that will receive and distribute protocols to other members of the Department Research Review Committee for review (if applicable)
- Organize a timely and efficient review process for protocols submitted in their department
- Ensure timely submission of protocols to the IRB
- Refer protocols to an ethics expert for review and recommendations when either the Chair or committee members believe it is appropriate

## What Are Additional Required Reviews?

Human Research protocols may require review and approval from entities not represented by the Principal Investigator's department responsible for the conduct of the research under the CWRU Human Research Protection Program policies. Human subject research conducted at CWRU which involve any of the following procedures (experimental or otherwise) will require additional review from the appropriate departments of committees prior to IRB approval:

- Biological hazards
- Human cell or tissue samples
- Select chemicals
- Stem cell use
- Controlled substances
- Biologics
- Electrical device use
- Ionizing radiation
- Lasers

If additional reviews are required, documentation of the additional approval should be submitted to the IRB before the IRB will approve the research. In general, documentation can be provided via ancillary review sign-off.

Examples of departments and committees that may be required to conduct additional reviews of Human Research proposed for conduct at CWRU are listed below. Additional internal and/or external entities not listed below may also be required to review proposed human subject research as indicated by the CWRU HRPP Office.

## CWRU Departments/Committees Utilized for Additional Reviews

***Please note:*** In some cases, officials from the various review committees may contact the IRB directly to communicate concerns or provide documentation of approval. The IRB staff verifies that required documentation is on file prior to issuing an approval. Final approval of the protocol by the IRB may not be given until all required approvals are complete. Resubmission of continuing reviews does not require re-review by the special centers unless there have been changes in the protocol that would affect its specialized review (i.e., alteration of the level of risk or the addition of new procedures).



### ***CWRU Conflict of Interests (COI) Committee***

On an annual basis, all CWRU faculty members, and key study team members are required to complete a CWRU Conflict of Interests disclosure form. The form is designed to obtain information regarding participation in certain outside activities that could be determined as a Conflict of Interest.

[The Conflict of Interests Committee](#) administers the University's Policies on conflict of interest with the aim of preserving the integrity of the University and its members and maintaining compliance with applicable federal regulations, while respecting academic freedom and encouraging outside scholarly and entrepreneurial activities.

#### **Research Conflict of Interests**

Conflict of interests in research can take many forms – financial, institutional, fiduciary responsibilities, intellectual property (inventorship), proprietary, consultation, interpersonal, etc.

- If the CWRU COI Committee Office identifies a potential for an actual, potential, or perceived conflict of interest, the conflict may be managed, reduced, acknowledged, or eliminated at the CWRU COI Committee discretion with input from the conflicted investigator(s).
- The CWRU IRB has the final authority to decide whether the conflict of interest and its management, if any, allows the research to be approved.

Executive Director for the HRPP will work in collaboration with the CWRU IRB, the CWRU Conflict of Interests Committee, when appropriate. Principal Investigators share responsibility with the CWRU HRPP Office for ensuring compliance with policies and issued management plans on their projects.

In addition to any situation where there is a suspicion of a COI, the HRPP Office staff is responsible for performing an internal research COI review on all new industry-funded, PHS-funded, and investigator- initiated studies as well as all personnel changes when a new investigator is added to an Industry-funded or PHS-funded study. For more information on research COI identification and management, refer to [CWRU COI Policy](#).

#### ***Grants and Contracts Offices***

The Office of Research Administration's [Pre- and Post-Award Services](#) and the [School of Medicine's Grants and Contracts Office](#) must review all industry-sponsored protocols and research contracts for the purposes of ensuring coordination of legal review, ensuring that investigators follow fiscal guidelines, and ensuring regulatory compliance with research billing policies. Grants and Contracts Office approval is not required prior to IRB submission, although approval is required prior to subject enrollment.

#### ***Case Comprehensive Cancer Center Protocol Review and Monitoring Committee (PRMC)***

The Protocol Review and Monitoring Committee ([PRMC](#)) is responsible for reviewing the scientific merit, priorities, and progress of proposed and ongoing cancer/cancer-related human research conducted at CWRU. The PRMC review is required as an additional specialized review in conjunction with department review and any applicable committee noted above. In some cases, PRMC review will fulfill the “department review” requirement needed for IRB review of Human Research.





Protocols reviewed by PRMC must attach the PRMC approval letter with their IRB submission. The IRB will consider any issues raised by PRMC during their review.

### ***CWRU Human Stem Cell Research Oversight Committee (HSCRO)***

[The CWRU Human Stem Cell Research Oversight Committee](#) within the Office for Research Administration provides ethical guidance and technical support as it relates to all forms of stem cell research and translation to clinical practice. The Stem Cell Research Oversight Committee may be required to additionally review proposed Human Research to present insight regarding directed application of stem cell ethics in the complex array of cultural, social, political, and economic issues.

### ***Office of Pre-Award Services and Agreements***

The Office of Pre-Award Services and Agreements (PASA) within the Office of Research Administration (ORA) is responsible for the review and negotiation of data use agreements (DUAs) and data access agreements, which include shared or secondary data, and material transfer agreements (MTAs), which include discarded tissue, specimens, blood and cell lines. This office assists faculty members with the preparation and execution of these documents. Every DUA and MTA is required to be signed by an authorized signatory for the university; this can only be done by PASA. For more information see [Pre- and Post-Award Services | Office of Research and Technology Management | Case Western Reserve University](#) or contact [CWRU-DUA@case.edu](mailto:CWRU-DUA@case.edu) or [CWRU-MTA@case.edu](mailto:CWRU-MTA@case.edu)

### ***CWRU Environmental Health and Safety Office***

Please contact CWRU's EHS Office for consultation for use of biological hazardous materials or select chemicals in processing biospecimens or cell lines. For more information see [Environmental Health and Safety | Environmental Health and Safety | Case Western Reserve University](#) or contact [cwruehs@case.edu](mailto:cwruehs@case.edu)

#### ***Electrical Safety***

If the protocol involves subject contact with new or nonstandard (non-FDA approved) electrical equipment, the equipment and the protocol must be submitted for approval to the CWRU Environmental Health and Safety (EHS) Office. Electrical safety is also a requirement when the equipment's grounding is attached to the unit's casing. Each protocol must include sufficient information to determine whether electrical safety is an issue. The protocol must identify all experimental or investigational electrical equipment used in subject contact by manufacturer model and serial number (if known) and an IDE number (if applicable). The protocol must describe how the equipment is to be used, as well as its location. All equipment must be approved before use on participants. A copy of the approval should be submitted to the IRB with the protocol. Final approval by the IRB cannot be given until EHS Office approval is complete.

### ***Radiation Safety Committee Review***

Any protocol that uses ionizing radiation (such as x-ray, CT, scintigraphy, PET, SPECT, etc.) in human participants for research purposes outside standard clinical/dental care require review and approval by a Radiation Safety Committee Review. This requirement is based not on the nature of the procedure but on whether the person would receive the radiation only because they are participating in the research. Conversely, if the person would receive the radiation for their clinical/dental care, regardless of the enrollment status, RSC review is not required.



***University Hospitals Radiation Safety Committee (RSC)***

When a submission requires Radiation Safety Committee Review, the CWRU Radiation Safety Department asks the UH Radiation Safety Committee to evaluate human-use protocols.

Here are the Outlined Steps (also see [Radiation Safety Ancillary Review Help Guide.pdf \(case.edu\)](#)):

1. An email with the protocol, informed consent form and Radiation Use Application (found in the SpartaIRB system Library under Templates) is required to be sent to Ahmad Hatami (ahmad.hatami@uhhospitals.org) or Raymond Muzic (raymond.muzic@case.edu).
2. Once the Radiation Safety Committee has reviewed and approved the radiation part of the study, the study team will need to attach a copy of the signed application under “Other Attachments” of the SmartForm in the SpartaIRB system.

In the event of a disagreement whether the proposed radiation use is within the standard of care, the matter is brought to the RSC for evaluation. This evaluation includes input from the department proposed to perform the procedure that exposes humans to ionizing radiation.

***School of Dental Medicine***

***Finance Department***

The School of Dental Medicine (SODM) Finance Department must review all SODM protocols that involve clinical patient care to assess the need for a coverage analysis. Based upon national and local coverage determinations, the office will craft a coverage analysis for your trial to ensure that CWRU continues to meet research billing and compliance requirements. Office approval of your coverage analysis is required prior to study initiation and subject enrollment

***Process for Externally Funded Research That Involves Clinical Procedures***

Any School of Dental Medicine researchers proposing to engage in research involving clinical procedures performed in the Dental Clinic that would normally be billed to the patient and/or insurance are required to follow the process outlined below. The purpose of this process is to help ensure that sufficient funding is requested from the sponsor to cover any research-related procedure costs and that costs are correctly billed. Any Principal Investigator (PI) proposing research involving clinical procedures should complete the following steps to create the proposal budget:

**Step 1:** PI should first create a Study Schedule that lists each proposed study visit and all the procedures that will occur at each visit.

**Step 2:** The Study Schedule should be forwarded to [SODM Research Administration](#) for review.

**Step 3:** SODM Research Administration will provide the Study Schedule to the Cashier’s Office to review and confirm that the procedures listed are appropriate, have the correct coding, and reflect the correct procedure costs. The Cashier’s Office will sign off on the Study Schedule to confirm their approval.

**Step 4:** Using these approved procedure costs, Research Administration will work with the PI to create an overall budget for the project that can be used for submission to the sponsor, if needed.

**Step 5:** If the project is funded by the sponsor, the PI, Cashier’s Office, and Research Administration will meet before any work on the project begins to ensure proper setup and coordination within the Clinic’s patient management system.

**Please note:** For additional information see The School of Dental Medicine Assistant Dean, who maintains a copy of this plan.



***School of Dental Medicine Pharmacy/Dispensary***

The School of Dental Medicine Pharmacy/Dispensary has the sole responsibility for the procurement, storage, distribution, and control of all medications for patients at the School of Dental Medicine Clinic. The Department provides information and assistance on the clinical use, pharmacokinetics, administration, and adverse reactions of medications.

The School of Dental Medicine Pharmacy/Dispensary dispenses investigational only in accordance with the current protocol approved by the IRB. All investigational products are dispensed through the School of Dental Medicine. The conditions outlined in the request (documentation, storage requirements, temperature control) are monitored periodically by an independent group.

## CHAPTER 9 – Special Considerations

### When Should a Suicide Risk Mitigation Plan Be Included in a Protocol Submission?

If questionnaire responses could reasonably be construed to indicate depression, anxiety, suicidality, or psychological distress, the protocol must include a written and proactive plan for monitoring responses and mitigating participant risk.

In the event that a research study includes formal depression screening, an individual with clinical experience and expertise assessing for depression and suicide risk must be a study team member and must be prepared and available to conduct the relevant clinical assessment. Depression screening results should be reviewed and scored in real time (optimally in person at the time of survey completion, and if the survey is being completed remotely no later than 24-48 hours after completion of the screen) by qualified individuals who know the appropriate clinical cutoff for assessment. Any participant who screens above the clinical cut-off must be contacted by the study team member who is a qualified clinician (in-person contact at the time of screening is optimal, and if the survey is being completed remotely, by phone call, not email communication) and assessed for active suicidal ideation with a plan or intent.

- If assessment is negative, refer either to the participant's own mental health provider if they have one, or to community resources (study team must have a list prepared and included in the submission).
- If the assessment is positive for suicide risk, [Frontline](#) or an equivalent provider (Frontline is optimal in Cuyahoga County, 216-623-6888) and/or 911 must be contacted on behalf of the participant.

The informed consent must make participants aware that depression screening is included in the study, that the results will be assessed, and that the study team will reach out if appropriate. In addition, the informed consent must be transparent about the mitigation plan in the case of active suicidal ideation with a plan or intent. A phone number for the participant must be obtained as part of the data set. The HIPAA section must include possible sharing of information with Frontline (or equivalent provider). The protocol must include a detailed mitigation plan as part of the study procedures to address clinically significant depression scores and suicidal crisis.

### What Are Considerations for the Informed Consent Process of Studies that Include ONLY Questionnaires/Surveys?

The need for written informed consent for questionnaire studies will vary depending on the involvement of the subject and the nature of the information being collected.

- An information sheet may be substituted for the written consent, indicating the nature of the study, the time requirement for the subject, and other information required for consent.
- The information sheet must indicate that completion of the questionnaire implies consent.
- A protocol must contain specific justification of the use of an alternative (i.e., information sheet) to written informed consent.
- The use of an information sheet **requires an IRB waiver of the need for written consent.**  
**Please note:** The use of REDCap or Qualtrics for electronic surveys with data transfer to with CWRU's Box Account is recommended.

## What Is Required for Focus Groups or Interview Studies?

It is important that the training and supervision of moderators and/or interviewers involved in focus groups and interviews is thoughtfully considered. When submitting studies that propose to use group discussion or interpersonal interviews, please include the training and supervision plans for the moderators or interviewers.

A script or outline of discussion topics or interview questions that reflect the overall structure of the group or interview must be submitted as a supporting document with the study protocol.

When focus groups or interviews are discussing sensitive topics, extra attention should be paid to privacy and confidentiality concerns.

Focus group sessions should open with a discussion about group standards and expectations. The consent for focus group studies should include statements that address the following issues.

- The risk of inappropriate behavior or interpersonal discomfort. Other group members may say or do something that make participants uncomfortable. It is important to start the first session with a group agreement regarding behaviors during discussions. Participants should be told that if another member makes them uncomfortable or approaches them outside of the group, the study team or moderators should be informed.
- The limits of confidentiality given the group setting. While researchers can take precautions to maintain confidentiality, the nature of focus groups prevents the researchers from guaranteeing confidentiality. Participants should be reminded to respect the privacy of fellow participants and not repeat what is said in the focus group to others.

Please note: Focus group and interview study consents should include statements that address the legal or ethical requirements to report to the appropriate individuals and authorities any information that is disclosed concerning child or elder abuse or neglect or potential harm to the participant or others.

### ***Audio Recordings***

Often investigators wish to record and transcribe focus group or interview sessions. This information must be documented in the consent. If outside transcriptions services will be utilized, this must also be disclosed in the consent section.

- All audio or video records of participants should be treated as private information.
- Facial images and voice prints are both considered identifiable information.
- Further, conversations often inadvertently contain elements of private information such as names or dates.

Therefore, these records need to be obtained and stored securely according to CWRU UTech's [requirements](#).

The study protocol should explain in detail how audio and/or video recordings will be collected, stored, transcribed, and destroyed. Consent/assent forms should describe these procedures in lay terms. Additionally, participants should have the option to agree or not agree, in the form of checkboxes, to be audio/video recorded and protocols and consent/assent forms should outline participant recording requirements (i.e., whether agreeing to be recorded is a requirement of participation) and alternatives (i.e., detailed notes can be used in place of audio/video recording).



Recordings should not be shared with external transcription services without an appropriate legal agreement. Please contact ORTM [Pre- and Post-Award Services](#) to establish a transcription service contract.

Please note: Cell phones are not permitted to record interviews or focus group discussions; only encrypted, password-protected devices may be used. Please see UTech's website for additional information. <https://case.edu/utech/departments/research-computing/about-us>

## What Are Considerations for Blood Drawn for Research Purposes?

All blood drawn for research purposes must be done with an IRB approved research protocol and consent plan. Written consent for venous blood drawing should include the amount of blood in lay terms (teaspoons, tablespoons, ounces, or cups), the number of samples, the number of needle sticks, whether an indwelling catheter will be used, and risks of infection, discoloration, and pain. Consent forms should indicate what will be done with the blood including what will be measured, how long the blood will be stored, and whether results will be available to the participants. If personal identifying information will be removed from the sample this should be stated along with whether or not these samples may be used in future research studies.

When research participants are acutely ill and subject to multiple clinically indicated blood tests, the investigator must discuss in the protocol what measures will be taken to ensure that research samples will not cause the total amount of blood removed (including clinical samples) to exceed the allowed limit. This applies to both children and adults.

Studies involving arterial blood drawing of any amount require written consent and must include the amount of blood in lay terms, a statement that a test for patency of collateral circulation (Allen test) will be performed, and the risks involved, i.e., gangrene, blood clot, possible loss of limb, as well as infection, discoloration and pain.

Studies that include a blood draw for research are typically required to obtain signed consent. Multiple blood drawing, regardless of amount of blood to be drawn, will always require written consent and/or assent.

### ***Adults***

Protocols typically may take a single collection of blood up to one unit (475 ml). Participants may repeat participation in a single blood draw study as long as more than 475 ml is not taken within 2 months (including clinical and research samples); however, consent must be obtained for each blood draw and this possibility must be discussed in the protocol. In general, a signed consent is required for blood draw studies. Pregnant women will have additional considerations.

### ***Children***

Extra blood sticks should be minimized whenever possible. Investigators should align research bloods draws with clinical blood draws or, if already placed for clinical purpose, IV or lines should be used. When enrolling children as controls, blood samples must be obtained at the time of clinical blood draws and the enrollment of minors must be justified. Research that obtains blood draws from minors who are less than two years of age or seeks to collect blood more than twice a week, will be subject to Full Board review.



General guidelines for blood draws in children include:

Timeline	Total Blood Volume*
Over 24 Hours	No more than 2ml/kg
Over 4 Weeks	No more than 3ml/kg
Over 8 Weeks	No more than 4ml/kg

\*Blood volume should include both clinical and research blood draws

In any case, Investigators should consider the overall health of the child participant and the amount of blood they will obtain and limit, when possible, blood draws in sick patients (e.g. anemia, low cardiac output, pulmonary or hematopoietic problems). Please be aware that extra monitoring and mitigation plans may be necessary if enrolling a particularly sick population or taking a large volume of blood.

### ***Research Samples Requiring Additional Venipunctures***

If extra blood samples are obtained for research purposes, written consent and assent are required. As a general rule, blood samples for clinical plus research purposes should not exceed 5cc/kg over 2 months.

### ***Multiple Samples***

Frequent blood draws, such as those commonly used for pharmacokinetic studies, should be done through indwelling access and not multiple venipunctures.

## What Are Considerations for Studies Involving DNA and Genetics (Blood and/or Tissue)?

All studies using blood or tissues for DNA or genetic studies (excluding discarded, anonymous tissue studies) must discuss in their protocols and consent forms how data will be kept confidential.

- The protocol and consent form must discuss what results, if any, will be told to the participant.
- In regard to paternity issues, it may be appropriate to include the disclaimer statement “It is the policy of this institution not to report information regarding paternity.”
- If the genetic studies are only a part of the protocol, participants should have the option to agree or not agree, in the form of checkboxes, to participate the genetic part of the study.
- Participants cannot be asked to sign away any rights to such materials. Consent forms must discuss future use of samples and data.
- Further details and suggested consent language are contained in the [Biomedical Consent Form Template](#).

## What Are Considerations for Studies That Include Chart Reviews?

The CWRU IRB will review and approve studies involving chart reviews or discarded tissues/cell lines/blood Studies must be reviewed and approved by the IRB prior to commencing research activities. All applicable federal regulations for the protections of Human Research apply. If children are involved, parental permission and assent must also be obtained unless the criteria for waiving parental permission and waiving assent are met. Additionally, for chart reviews involving other vulnerable populations, [45CFR46, Subparts B, C, D](#) may also apply.



The IRB's main concern with chart reviews for research is the possible invasion of privacy and the use of confidential and privileged data or information. As such, the following items should be considered and addressed:

- The Data Safety Plan Section of the SpartaIRB protocol template should outline how the data will be received, stored and shared (if applicable).
- CWRU's UTech Department should be contacted for a consultation to help with the Data Safety Plan.
- UTech prefers researchers to keep their identifiable data, including any of the HIPAA identifiers, in REDCap, CWRU's BOX, or CWRU's Secure Research Environment (SRE) Network
- Investigators are required to state the specific secure data storage location and attach to their submission a copy of the data collection sheet and corresponding linking sheet.
- The data collection sheet should not contain any elements of PHI.
- All elements of PHI should be on the linking sheet. The two sheets should both contain a unique study number that is not derived from any patient identifiers.

For any study to qualify as a chart review, all data accessed must have been collected (or will be collected) as part of routine clinical care or institutional operations (e.g., student records, employee records, etc.).

- Informed consent must be obtained unless a waiver can be fully justified and meets the regulatory requirements.
- If an investigator has support to obtain consent from a participant and, if practicable, according to applicable regulations they must do so as usual under the Human Research Protection regulations. The consent process and all requests for waivers must be addressed in the protocol/research plan.

### ***Contact with Potential Participants from Chart Reviews***

Any investigational or research project involving use or review of charts/records where contact will be made with participants or participants' families as a result of chart review requires approval by the IRB. No one can be contacted to participate in research without approval from the data source. If seeking approval from a data source, the lack of reply can never be construed as approval. The investigator is required to submit a protocol application to the IRB indicating:

- Justification for contacting participants;
- Method of contact; and
- Indication that prior approval will be obtained from the data source, including documentation that indicates permission to access data and/or actual participants.

### ***Can Chart Reviews Fall Under the Exempt Research Category?***

Certain chart review studies may qualify for an IRB exemption; however, an investigator can request an exemption but cannot make that determination. An exemption, if eligible, can only be made by the CWRU IRB after a formal exemption application has been submitted and reviewed.

### ***Can An Investigator Access Their Own Patient Records for Research?***

Investigators in clinical practice (i.e., physicians, dentists, social workers, nurses) may access their own patients'/clients' existing records (or those of their group practice) for research; however, the IRB requires additional documentation. Such documentation includes IRB approvals, letters of cooperation, and/or requests for appropriate waivers or consents/parental permissions. As part of the protocol application, the investigator must ensure that all collected data will be kept confidential and private, and any study results will be presented in a way that preserves subject anonymity.



### ***How Can An Investigator Gain Access to Another Investigator's or Another Organization's Records for Research?***

Investigators may access data from another source. However, the protocol application submitted to the IRB must describe how patient privacy will be protected and how the confidentiality of the information will be maintained. Best practice recommendations are for the investigator to receive completely de-identified and unlink-able data from the data source. If this is not possible and a member of the research team must review the charts/electronic records, then investigators reviewing the charts/records must agree to keep all identifying data confidential. If identified data leaves a data source, then consent from participants is usually required before they (or their data) are included in the study.

## **Research Repositories**

Data registries or biorepositories are protocols that describe the collection of data and/or samples specifically for future research. The establishment of either data or sample repositories for research must, therefore, consider the procedure for future use of those data or samples.

When reviewing the proposed repository, the IRB will require a plan that describes:

- Circumstances under which data or samples will be shared, and with whom they will be shared
- Process by which researchers should request data and/or samples (for example, the form that researchers will use to request data and/or samples)
- How decisions will be made to grant requests
- Whether data/samples can be shared outside of the institution
- Whether data/samples will be shared in a de-identified, linked/coded, or identifiable way
- Attestation that no data or samples will be shared without verification of IRB review of the proposed use

Consent forms for repositories should always include information about how data and samples will be used for future research, and any applicable options for consent of future use.

When researchers submit projects to the CWRU IRB to use data or samples from established repositories, the CWRU IRB will request documented permission from the repository.

## **Pilot Studies**

A pilot study is generally defined as a small-scale, preliminary study to help design methods and procedures to be used within a larger clinical trial. Pilot studies that include participants or data and involve an intervention or interaction for purposes of collecting or sharing data require IRB review regardless of the size of the study or the intent of the investigator.

## **Clinical Trials**

A clinical trial is a research study in which one or more human participants are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.



If the study is a clinical trial and supported by a [Common Rule agency](#), one IRB-approved version of a consent form that has been used to enroll participants must be posted on a public federal website designated for posting such consent forms. The form must be posted after recruitment closes, and no later than 60 days after the last study visit. Please contact the study sponsor with any questions.

Please see **Chapter 26** for a full description of the ClinicalTrials.gov requirements.

## CHAPTER 10 – General Requirements for Informed Consent

### Definitions Pertinent to the Informed Consent Process

**Adult:** A person who has 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. The specific treatments or procedures involved in the research and the jurisdiction in which the research will be conducted may determine who is considered an adult.

**Assent:** A child's affirmative agreement to participate in research. Failure of a child to object to participation cannot be construed as assent. Assent is a process involving communication with the child. A signature on an assent document, a physical gesture of affirmation, or a verbal assent are not, in and of themselves, assent.

**Child:** A person, who has not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted. For example, in most American states, a child is someone age 17 and younger; however, in Taiwan, a child is someone age 19 and younger.

**Deception Research:** A study in which participants are intentionally misinformed or information is purposely withheld, as part of the research design, and therefore not all elements of informed consent can be provided. All required elements, except those that would expose the deception (that are purposely withheld), need to be included in the original informed consent document. All deception studies must include a clear and detailed debriefing process and a request for an alteration to the informed consent process.

**Guardian:** An individual who is legally authorized under applicable state or local law to consent on behalf of a child to general medical care. Foster parents cannot provide parental permission for their foster children to engage in research, only emergency medical care.

**Incapacity:** Lacking in the ability to make health care decisions, understand the benefits and risks of the proposed health care/research, understand possible alternatives, and make and communicate a decision.

**Informed Consent:** An individual's voluntary agreement, based upon adequate knowledge and understanding of the relevant information, to participate in research either for themselves or for a child for whom they are the parent or legal guardian.

**Legally Authorized Representative (LAR):** An individual, judicial, or other entity authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research. The term Legally Authorized Representative may include a person properly appointed by an advanced directive (such as a living will or declaration) or a durable power of attorney for health care, certain court appointed guardians, and next of kin. Documentation of a person's status as a LAR for a research participant is required and must be carefully evaluated to determine the validity of the appointment and scope, if any, of authority granted to make decisions regarding procedures involved in the research. For example, the existence of a durable power of attorney for health care or advanced directive for health care may not create a LAR for any or certain kinds of research decisions. The University's Office of General Counsel shall be



consulted by the IRB and investigator if there are any questions related to Legally Authorized Representative's consent.

## Principles of Informed Consent

The CWRU IRB Informed Consent Guidance is based upon the essential principles established in [The Belmont Report](#): respect for persons, beneficence, and justice; and is in accordance with the Department of Health and Human Services ([DHHS](#)) ([45 CFR 46.116](#)). Informed consent (respect for persons) is one of the primary ethical requirements governing research that involves human participants. The concepts of informed decision-making and that of voluntary participation are essential elements of the informed consent process. To ensure an effective informed consent process, the consent form should express the realistic expectations of participation in the research study, avoiding inducement by raising false hopes.

In order to decide whether they wish to participate or continue to participate in a research study individuals must be given all of the relevant information about the research. The informed consent process should also include opportunities to allow potential participants to ask questions and to exchange information freely with the study staff. Moreover, investigators have an ethical and contractual responsibility to keep research participants fully informed of any new information that may affect their willingness to continue to participate. The consent document should therefore be the basis for a meaningful exchange between the investigator and the potential research participant.

## What Guidelines Should PIs and Study Staff Follow to Ensure Comprehension During the Informed Consent Process?

It is the Principal Investigator and study team members' ethical responsibility in research to disclose information to a potential research participant and to ensure that the person has the capacity to reach a decision based on the information provided. Obtaining valid informed consent is a necessary component in the research process. See Appendix B for Ensuring Comprehension during the Informed Consent Process for details.

The IRB requires that the informed consent documents for non-exempt research include the **nine basic elements** of informed consent listed below ([45 CFR 46.116\(a\)](#) and [21 CFR 50.25\(a\)](#)).

The IRB may also require any or all of the **six additional elements** of informed consent ([45 CFR 46.116\(b\)](#) and [21 CFR 50.25\(b\)](#)), depending on the nature of the research.

## What Are the General Requirements for Informed Consent Form of Non-Exempt Research?

In addition to the nine basic elements listed below, a **Key Information Section** at the beginning of the informed consent form is required.

- The aim is to put the important information in a section at the beginning of the form
- The Key Information Section will include information about the purpose, risks, benefits, and alternatives and will explain to the person how to think about these pieces of information in terms of making a decision about study participation.
- It should be presented in a concise and focused manner.





- The ***Basic Elements Section*** of the consent form will repeat the information found in the Key Elements section.

## What Are the Nine Basic Elements of Informed Consent?

### 1. ***Research Statements***

The research statements must include the following:

- Statement that the study involves research
- Explanation of the purposes of the research
- Explanation of the expected duration of the participant's participation
- Description of the procedures involved; -AND-
- Identification of any procedures that are experimental.

It is important to explicitly state that the individual is being asked to participate in a research study so as to clearly differentiate the relationship between participant and researcher from student and teacher or physician and patient (for example) and informed consent for participation in a program or non-research activity from the informed consent for research.

### 2. ***Risks and Discomforts***

A description of any foreseeable risks and discomforts. These include but are not limited to potential physical, psychological, emotional, and social risks and discomforts.

### 3. ***Benefits***

A description of any benefits to the participant or others that may reasonably be expected from the research. Payment for participation is **not** considered to be a benefit. If the participants are remunerated for participation, the details must be included separately from benefits. Remuneration includes both reimbursement for expenses and incentives for time and discomfort. Most Social Behavioral studies do not include direct benefits. It is required to state that there are no direct benefits, if applicable. If uncertain, contact the IRB office at [cwru-irb@case.edu](mailto:cwru-irb@case.edu)

### 4. ***Alternatives***

A disclosure of appropriate alternative procedures or courses of treatment, if any, including those that might be advantageous to the participant. It is appropriate to state that an alternative is to not participate in the study.

### 5. ***Confidentiality***

A statement describing the extent, if any, to which confidentiality of the records identifying the participants will be maintained. Specific language can be found in the consent template.

### 6. ***Compensation and Research-Related Injury***

Research involving more than minimal risk must include an explanation as to whether any compensation and/or medical treatments are available if injury occur and, if so, what they consist of or where further information may be obtained.

Included in the standard language required by the CWRU IRB is the obligation of the investigator to direct a research participant experiencing physical injury or illness as a result of participating in a study to appropriate medical care.



If compensation for injury is available from the study sponsor or funding agency, this should be explained in the body of the consent form. This must be consistent with any executed contracts that might exist.

**7. *Contact Person***

An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to participants. Include contact information such as phone numbers and email addresses.

**8. *Voluntary Participation and Right to Withdraw***

A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled. If applicable, student subject populations must be told that their grades or class standing would not be adversely affected. If applicable, employees must be told that their supervisors may be aware of their participation during work hours but would never learn of their responses. It is also appropriate to include a statement that if a participant withdraws from the study, they may be contacted to determine their reason(s) for withdrawal but that an explanation is not necessary.

**9. *One of the Following Statements About Any Research That Involves Collection of Identifiable Information or Identifiable Biospecimens:***

- A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility -OR-
- A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

## What Additional Elements Must be Included When Appropriate?

- A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to participants and if so, under what conditions.
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

## What Are the Six Additional Elements of Informed Consent?

When applicable, the additional elements of informed consent must be included in the consent document. Below is a description of each of the elements, as well as guidance to when they are required. The main determination is whether the additional information will have an impact on a participant's willingness to voluntarily participate in the research, and whether the information is meaningful and protects their rights and welfare. Please contact the IRB Office for guidance at [cwru-irb@case.edu](mailto:cwru-irb@case.edu)



**1. *Unknown Risks***

A statement that the particular treatment or procedure may involve risks which are currently unforeseeable to the participant (This is required if the research involves any procedures that are not well known).

**2. *Termination of Participation***

Investigators must describe any anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent. This is usually only done when the safety and welfare of the participant is in question. (This is required if there are any anticipated circumstances under which a participant's participation may be terminated without the participant's specific concurrence).

**3. *Costs***

Any additional costs to the participants that may result from participation in the research. This is only required if there are any anticipated additional costs directly related to the research. This should be consistent with any grants or contracts that might exist.

**4. *Consequences of Withdrawal***

The consequences of a participant's decision to withdraw from the research must be described by the investigator if there are any potential adverse consequences for a participant, as well as the specific procedures for orderly termination of participation by the participant (which must also be described in the protocol).

**5. *New Findings***

If applicable, a statement that significant new findings developed during the course of the research which may relate to or affect the participant's willingness to continue participation will be provided to the participant.

**6. *Number of Participants***

The approximate number of participants to be involved in the study. If the study is a multi-center study, indicate how many sites are involved, how many participants will be included overall, and how many will be included at this site.

***Additional Consent Form Requirements***

**• *No Exculpatory Language***

No informed consent, whether written or oral, may contain any exculpatory language through which the participant or their legal authorized representative is made to waive or appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

## What Is CWRU IRB's Standard Research Consent Language?

It is the requirement of the IRB that the Standard Research Consent Language be included in all written consent forms unless specifically waived by the IRB.



***FDA language:***

“If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records.”

- If the research is not being regulated by the FDA, the sentence above can be deleted.

***ClinicalTrials.gov:***

Research considered an **Applicable Clinical Trial (ACT)** by the FDA must include the following statement somewhere in the consent form:

“A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”

For **non-ACT** studies registering with ClinicalTrials.gov the statement is not required to reference U.S. law because most of these studies are required to register on the ClinicalTrials.gov site due to a condition of their grant or for publication purposes:

“A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”

- If the study is not being registered on ClinicalTrials.gov, the sentence above can be omitted.

***NIH Data Management & Sharing Policy / Sharing of Data/Biospecimens***

In order to meet NIH requirements and other studies that will share data with other researchers at internal or external institutions or data repositories the following language should be added to the informed consent form as applicable:

**Sharing of de-identified data or specimens:**

“This study is collecting data and/or biospecimens from you. We would like to make these available for other research studies that may be done in the future. The research may be about similar diseases or conditions to this study, but it could also be unrelated. These studies may be done by researchers at this institution, other institutions, including commercial entities. Our goal is to make more research possible.

Your de-identified information and/or samples may be shared with other researchers or databases. If your identifying information is removed from the data or biospecimens you provided, they may be shared without your additional consent. We cannot guarantee anonymity of your personal data even if identifying information is removed.”

[Add the statement below if the data and biospecimens to be shared might be coded or identifiable]

**Optional sharing of identifiable or coded data or biospecimens:**

“In addition, with your consent, we would like to share your identifiable or coded data and other biospecimens with other researchers for future research.

Coded data means personal identifiers are removed but a link to your identity exists. We will protect the confidentiality of your information to the extent possible. Coded information may also be submitted to federal or other databases/repositories. Identifiers and PHI that will be shared for future research purposes includes [INSERT IDENTIFIABLE OR PHI INFORMATION THAT WILL BE SHARED FOR FUTURE RESEARCH STUDIES. EXAMPLES: UNIQUE STUDY IDENTIFIERS, DATES, ZIP CODES, ETC.]

It is your choice whether or not to let researchers share your coded data and biospecimens for research in the future. If you change your mind and no longer wish to have us store or share your identifiable/coded data and biospecimens, you should contact [INSERT LOCAL OR COORDINATING RESEARCHER CONTACT]. We will do our best to honor your request and retrieve any data and biospecimens that have been shared with other researchers or databases. However, there may be times we cannot. For example, if the data and biospecimens have already been used for new research.

Do you agree to allow for the sharing of your identifiable/coded data and biospecimens?

\_\_\_\_\_ YES, use my identifiable/coded data and biospecimens in other research studies.

\_\_\_\_\_ NO, do NOT use my identifiable/coded data and biospecimens in other research studies.”

## What Are the CWRU IRB Consent Requirements?

### **1. *Authorization to Use and Disclose Protected Health Information (PHI) for Research Purposes***

All research studies enrolling patients or collecting protected health information (PHI) must abide by the Health Insurance Portability & Accountability Act (HIPAA) enacted April 14, 2003. This regulation, also known as the “Privacy Rule,” establishes conditions under which researchers may have access to and use an individual’s PHI to for research purposes. Clinical HIPAA Authorization DOES NOT cover use or disclosure of PHI for research purposes. Permission must be obtained via signed authorization for use and disclosure of PHI for research purposes. The IRB requests that the language relating to HIPAA and authorization for use and disclosure is included in the consent document. Please reference the HIPAA Authorization template for the approved language.

### **2. *Signature Section***

The signature section of the Standard Research Consent Language has signature blocks for the following study categories: adults able to provide informed consent; adults with decisional impairment; minors where the IRB has determined that the permission of one parent is sufficient; and children where the IRB has determined that the permission of one parent is not sufficient unless the other parent is deceased; unknown; incompetent; not reasonably available; or one parent has legal responsibility for the case and custody of the child. The person obtaining consent must both sign and print their name. If the Principal Investigator does not obtain consent, they must confirm the eligibility of the participant and verify that consent was obtained by signing and dating the consent form within one month of when consent was obtained.

### **3. *No Omission of Required Elements Unless Waiver Approved***

The investigator must indicate in the protocol application the type of consent used with the study, including whether a waiver of consent is being requested, and the assent plan for children (if applicable). Required elements of informed consent may not be omitted unless waived by the IRB. Requests for waivers need to be justified in the protocol.

### **4. *Use of First or Second Person Language***

The language of the consent document should be consistent throughout with the use of either the first person pronoun (i.e., “I, me, my”); or second person pronoun (i.e., “you, your”). The IRB strongly encourages the use of second person; however, first person consent forms are allowed.



**5. *Language Level***

Informed consent documents must be written in language that is at the appropriate reading and comprehension level for the targeted population. The target language level for consent forms must read at no greater than an 8th grade reading level. Further, the language has to be age-appropriate and understandable. The IRB encourages investigators to use the IRB Consent template when developing consent documents. Use of a readability score tool is recommended. Two frequently used readability tools are Flesch-Kincaid and SMOG – these formulas can be accessed for free by searching online.

**6. *No Complex Technical Language/Jargon***

All consent and study documents must be in lay language and should not include complex language that would not be understandable to all participants. Technical and scientific terms should be adequately and clearly explained using common or lay terminology. The IRB prefers the use of only the lay term. For example, “tooth decay” or “cavities” instead of “caries”; “germs” instead of “bacteria”; “heart attack” instead of “myocardial infarction.”

Generic names are preferable when describing certain items unless the brand name is more commonly known and understood. Regardless of which name is preferred, it should be used consistently throughout the informed consent documents. Devices and procedures should also be described consistently throughout the documents and explained in simple language. The IRB would allow the use of technical jargon depending on the study population. An example would be using medical terminology for a study population consisting of medical/dental students or professionals.

## What Are General Requirements of the Informed Consent Documents?

There may not be discrepancies within the informed consent documents, the IRB application, the sponsor’s or investigator’s protocol, the investigator’s brochure, the grant and/or the contract regarding the purpose, risks, and benefits of the research. The Informed Consent document must be in a language understandable to the participant or the participant’s legally authorized representative ([45 CFR 46.116](#) and [21 CFR 50.25](#)). The IRB recommends that readability should not exceed eighth grade reading levels.

Verbal or telephone consent is not acceptable unless the IRB has specifically waived the requirement for a written consent ([45 CFR 46.116\(c\)](#)). Consent must be obtained before initiation of any study procedures unless delayed consent is approved by the IRB through a waiver of consent. The investigator must provide a detailed description of the intended method for obtaining informed consent in the protocol. All informed consent documents (full written documents, oral scripts, assent forms, short form, etc.) must be submitted for review and approval by the IRB prior to use. Any changes in the informed consent documents must be submitted as a modification to the IRB for review and approval prior to use.

The location and timing of the informed consent process must ensure privacy and sufficient time for the potential participant to make a decision. Additionally, the circumstances must ensure that the potential participant is not under mental or emotional duress or in physical pain, or scientifically justify any deviation from this plan.

No informed consent, whether written or oral, may contain any exculpatory language through which the participant or their legal authorized representative is made to waive or appear to waive any of the participant’s legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.





For all research involving test articles regulated by the U.S. Food and Drug Administration (FDA), informed consent documents should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies are not appropriate when the purpose of the study includes determination of safety. In studies that also evaluate the effectiveness of the test article, informed consent documents should include that purpose but should not contain claims of effectiveness. In addition, participants need to be informed that their records may be inspected by the FDA.

No unproven claims of effectiveness or certainty of benefit, either implicit or explicit, may be included in the informed consent documents.

When the IRB approves a protocol and waives the requirements for obtaining a signed informed consent document, the meeting minutes must document the required regulatory determinations made by the IRB in accordance with the above criteria as well as including the protocol-specific information for the justification of the waiver.

## How Is the Health Insurance Portability and Accountability Act (HIPAA) Authorization to Use and Disclose Protected Health Information (PHI) for Research Purposes Used in the Informed Consent Document?

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was written to allow for insurance portability but also as a Privacy Rule to protect the privacy and security of a person's identifiable health information. The purpose of this guidance is to provide researchers with the information they will need to comply with the Privacy Rule associated with HIPAA.

The HIPAA Privacy Rule establishes the conditions under which Protected Health Information (PHI) may be used or disclosed by covered entities for research purposes. CWRU is a hybrid entity and as such, must abide by the HIPAA Rules for the use and disclosure of PHI under its jurisdiction (see [45 CFR Part 164](#)) for related purposes. CWRU and its affiliated hospitals empower their IRBs to act as Privacy Boards on behalf of each Covered Entity.

## When Can a Waiver or Alteration of the Informed Consent Process Be Granted?

When reviewing Human Research subject to the revised Common Rule, the CWRU IRB will evaluate requests for waivers or alterations of informed consent in accordance with the requirements and criteria specified in the revised rule and summarized below. The IRB's determination will be documented in the IRB record and communicated to the investigator.

**A Waiver or Alteration of the Consent Process** is defined as a variation from the traditional informed consent process. For example, this may include an alteration or omission of some elements of the consent process, a waiver of consent documentation (participant signatures), or a full waiver of consent (consent will not be obtained). However, this process still includes a considerate and thorough discussion of the study with the participant and verification that the participant understands the study and will participate voluntarily.



***What is a Waiver of Signed Written Consent or Waiver of Written Documentation?***

If CWRU IRB waives documentation of informed consent, the investigator still needs to obtain informed consent from the study participant but does not need to document the circumstances of that consent on paper (i.e., verbal consent).

If the IRB has waived written informed consent, an information sheet or written script for verbal use is required. The information sheet/written script must include all the required elements of consent disclosure and be approved by the IRB prior to its use.

CWRU IRB may waive the requirement for the investigator to obtain a signed consent form for some or all participants if the IRB finds:

- That the only record linking the participant to the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality, ([45 CFR 46 117\(c\)\(1\)](#)), and the research is not subject to FDA regulation -OR-
- If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm -OR-
- That the research presents no more than minimal risk or harm to the participants and involves no procedures for which written consent is normally required outside of the research context ([45 CFR 46 117\(c\)\(2\)](#)).

When CWRU IRB waives the requirement to obtain written documentation of the consent process, the IRB will review a written script of the information to be provided to participants. This script must include all the required and appropriate elements of consent disclosure. The investigator will provide the participants with a copy of the script unless the IRB determines that this is not possible, or that a copy of the script will not add to the protections of the participants.

CWRU IRB may approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. **In order to approve such a waiver or alteration, the IRB must find and document the following:**

1. The research involves no more than minimal risk to the participants
2. The research could not practicably be carried out without the requested waiver or alteration
3. The waiver or alteration will not adversely affect the rights and welfare of the participants
4. Whenever appropriate, the participants or LARs will be provided with additional pertinent information after participation -AND-
5. The research is not greater than minimal risk under the FDA regulation

Investigators will be asked to provide justification, or additional information or documentation, to support that the above criteria are satisfied.

**Waiver or Alteration of Consent in Research Involving Public Benefit and Service Programs**

The IRB may approve a consent procedure for public benefit and service programs which does not include, or which alters some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds *and documents* that:

- The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
  - Public benefit or service programs
  - Procedures for obtaining benefits or services under those programs



- Possible changes in or alternatives to those programs or procedures -OR-
- Possible changes in methods or levels of payment for benefits or services under those programs; -AND-
- The research could not practicably be carried out without the waiver or alteration.

### ***What Are the Requirements for Partial Waivers of Consent for Screening, Recruiting, or Determining Eligibility [\[§46.116\(g\)\]](#)?***

The revised Common Rule removes the requirement for partial waivers of consent for the use of information or specimens for the purposes of screening, recruiting, or determining the eligibility of prospective participants for inclusion in the research. Pursuant to the revised rule, the CWRU IRB may approve a research proposal in which an investigator will obtain information or biospecimens for these purposes without the informed consent of the prospective subject or the subject's LAR if either of the following conditions is met:

1. The investigator will obtain information through oral or written communication with the prospective subject or LAR, or
2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

When research is subject to the revised Common Rule, and the above conditions are met, investigators do not have to request waivers of consent for the purposes of screening, recruiting, or determining eligibility but DO have to describe the activities in the application or protocol submitted to the IRB. The above does not negate the requirements of other rules, such as HIPAA, when applicable. It also does not negate the requirement to obtain consent, or a waiver of consent, before involving a subject (including the use of their identifiable private information or biospecimens) in other research activities.

### **What Are Requirements for Consenting and Debriefing for Deception Studies?**

The IRB may allow the alteration of informed consent in research involving no more than minimal risk, which can only be conducted when participants are less than fully informed, and the missing information does not increase participant risk (e.g. behavioral and/or deception studies). In these situations, the IRB may determine that consent, which does not disclose information about all elements of informed consent, can be obtained for initial enrollment. However, on completion of the research, or after participation, each participant must be informed of the true nature of the study and be offered the ability to decline participation. The records must document why the IRB judged that each criterion listed above was met for the protocol. Research that includes participant deception is not eligible for exempt review.

### **What Are the Requirements for Working with Schools in Research Projects?**

Research involving the use of student educational records is reviewed and conducted in accordance with the Family Educational Rights and Privacy Act (FERPA), [34 CFR Part 99](#). The IRB Review Checklist FERPA/PPRA is used to conduct this review.

The process to grant exceptions to parental/student consent to release student records for research is describe below. This responsibility may be delegated to the IRB.



- An educational agency or institution may disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:
  - Develop, validate, or administer predictive tests.
  - Administer student aid programs.
  - Improve instruction.

A **school district or postsecondary institution** that uses this exception is required to enter into a written agreement with the organization or researcher conducting the research that specifies:

- The determination of the exception.
- The purpose, scope, and duration of the study.
- The information to be disclosed.
- That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements [in 34 CFR 99.31\(a\)\(6\)](#) on re-disclosure and destruction of information.
- That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the organization with legitimate interests.
- That the organization is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study.
- The time period during which the organization must either destroy or return the information.

Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

- Student's name and other direct personal identifiers, such as the student's social security number or student identification number.
- Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address and personal characteristics or other information that would make the student's identity easily traceable; date and place of birth; and mother's maiden name.
- Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.
- Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

### ***What Is the Process to Comply with the Protection of Pupil Rights Amendment?***

- Prior consent means:
  - Prior consent of the student, if the student is an adult or emancipated minor; or
  - Prior written consent of the parent or guardian, if the student is an un-emancipated minor.
- Schools and contractors obtain prior written parental consent before minor students are required to participate in any ED-funded survey, analysis, or evaluation.
- For research not funded by the US Department of Education: The IRB must verify compliance with U.S. Department of Education regulations that schools are required to develop and adopt policies in conjunction with parents regarding the following:



- The right of a parent of a student to inspect, upon the request of the parent, a survey created by a third party before the survey is administered or distributed by a school to a student.
- Any applicable procedures for granting a request by a parent for reasonable access to such survey within a reasonable period of time after the request is received.
- Arrangements to protect student privacy that are provided by the agency in the event of the administration or distribution of a survey to a student containing one or more of the following items (including the right of a parent of a student to inspect, upon the request of the parent, any survey containing one or more of such items):
  - Political affiliations or beliefs of the student or the student's parent.
  - Mental or psychological problems of the student or the student's family.
  - Sex behavior or attitudes.
  - Illegal, anti-social, self-incriminating, or demeaning behavior.
  - Critical appraisals of other individuals with whom respondents have close family relationships.
  - Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers.
  - Religious practices, affiliations, or beliefs of the student or the student's parent.
  - Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).
- The right of a parent of a student to inspect, upon the request of the parent, any instructional material used as part of the educational curriculum for the student.
- Any applicable procedures for granting a request by a parent for reasonable access to instructional material received.
- The administration of physical examinations or screenings that the school or agency may administer to a student.
- The collection, disclosure, or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student privacy that are provided by the agency in the event of such collection, disclosure, or use.
- The right of a parent of a student to inspect, upon the request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student.
- Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received.

## Electronic Informed Consent (eIC, e-Consent)

**For CWRU-specific guidance regarding the use of eIC, see [CWRU HRPP Guidance for Electronic Informed Consent \(eIC\)](#)**

Investigators are able to obtain consent electronically, and this process may substitute for paper-based informed consent. The electronic informed consent (eIC) must contain all elements and meet all regulatory criteria for informed consent outlined by HHS and FDA in [45 CFR 46.116](#) and [21 CFR 50.25](#). The eIC may contain hyperlinks and other electronic strategies to enhance comprehension but must be easy to navigate with sufficient time allowed for understanding, and the potential participants' electronic literacy must be considered. Assent may also be obtained electronically but the capabilities of the child to assent using electronic methods must be considered.





The process of informed consent requirements still apply with electronic consent, and the following must be included in the protocol:

- Measures to ensure that participants have access to all the consent related materials
- Plan to ensure all hyperlinks are active and working
- Plan for providing participants with a signed copy of the consent form
- Plan for how the date of the electronic signature will be captured

Electronic informed consent documents must exactly mirror the text and format of the current CWRU IRB-approved Informed Consent Form and/or Assent Form. All sections must be present and all formatting, such as bullet points, checkboxes, and signature and date fields, must be maintained to the extent possible within the electronic framework. Additionally, **the eIC should include the IRB Approval Stamp that includes the IRB Study Number, Approval Date, Effective Date, and Expiration Date.**

If the consent process takes place in person, then additional verification of identity is not required. However, “If any or all of the consent process takes place remotely and is not personally witnessed by study personnel, the electronic system must include a method to ensure that the person electronically signing the informed consent is the subject who will be participating in the research study or is the subject’s LAR (see [21 CFR 11.100\(b\)](#)).” Proposed methods for verifying identity (e.g. driver’s license, birth certificate, or security questions, for example) must be described in the study protocol and approved by the IRB, as well as methods for collecting electronic signatures. The submission may be referred to Research IT in order to verify security and compliance with 21 CFR part 11 before approval is granted. For more information on HHS and FDA regulations regarding eIC, see [Use of Electronic Informed Consent: Questions and Answers | HHS.gov](#)

When an electronic system is used there must be a time-stamped audit trail, full record retention (either electronic or paper), and the ability to provide copies and permit inspection ([21 CFR Part 11](#)). A copy must be provided to the subject.

## What Happens When Children Reach Age of Majority During Their Participation in a Study?

If the research involves children who will continue to undergo research interventions (including the collection of identifiable private information) after they reach the legal age to consent to the procedures involved in the research, the IRB research protocol should address how consent for continued participation in the research study will be obtained from these individuals at the time they reach such status. The IRB requires investigators to re-consent children who have reached majority as adults, except in unusual circumstances.

## What Are Additional Protections for Enrolling Decisionally Impaired/Cognitively Impaired Adult Participants in a Research Study?

For research studies in which the nature of the participant population is such that an individual may not be capable of initially providing direct consent for study participation **but may recover** adequate decision-making capability for direct consent at a later time, the IRB research protocol/informed consent document must address a mechanism whereby direct consent for continued participation in the research study will be obtained from the individual at the time they regain adequate decision-making capability.





If the nature of the participant population is such that an individual can **never** provide direct consent for study participation, then the IRB research protocol/informed consent document must address a mechanism whereby direct consent for continued participation in the research study will be obtained from the participant's parent, legal guardian, or legally authorized representative.

## What Is Documentation of Informed Consent [[§46.117](#)]?

It is the policy of the IRB to assure that for research involving human participants, provisions are made to obtain legally authorized informed consent from each prospective participant or legally authorized representative. However, the IRB may grant a waiver of informed consent if conditions presented are in accordance with the requirements for a waiver or alteration of informed consent. Any such waiver or alteration must be consistent with applicable Federal and Ohio state laws and regulations.

Unless the requirement for documentation of consent is waived by the IRB, informed consent must be documented by the use of written informed consent form (ICF) approved by the IRB and signed (including in an electronic format) by the subject or the subject's LAR. A written copy must be given to the person signing the ICF.

All approved informed consent forms must have the CWRU IRB stamp, which contain the CWRU protocol number, IRB approval date, IRB effective date, and the consent expiration date. The IRB requires that the most recently approved and non-expired consent documents be used when obtaining consent from participants.

The signature section of the CWRU Standard Research Consent Language has signature blocks for the following study categories:

- Adults able to provide informed consent
- Adults with decisional impairment
- Minors where the IRB has determined that the permission of one parent is sufficient -AND-
- Minors where the IRB has determined that the permission of one parent is not sufficient unless the other parent is deceased; unknown; incompetent; not reasonably available; or one parent has legal responsibility for the care and custody of the child. Both the research subject and the person obtaining consent must sign and print their names.

It is important to complete an Informed Consent Documentation Checklist during each consent process (an example template is available on the [CWRU IRB Guidance and Resources website](#)).

For more information regarding the Informed Consent Form, see Chapter 11.

## What Are the Principal Investigator's Responsibilities for Obtaining Consent?

The Principal Investigator for an IRB-approved study is ultimately responsible for the conduct of the study including the entire informed consent process and the instruction and oversight of individuals who may be involved in this process.

- Informed Consent must be obtained from a human subject or their legally authorized representative (i.e.; parents, court appointed guardian, or legally authorized representatives of those unable to give consent due to age, physical, or mental incapacity) and assent, when possible, from participants who



cannot give consent (i.e.; children seven years of age or older) prior to conducting the research. The Principal Investigator is held accountable to guarantee that informed consent is obtained from every participant according to their approved IRB protocol.

- Open communication between the participant and the person obtaining consent is vital. This includes a thorough explanation of the purpose of the research project, the procedures to be followed, and the risks and possible benefits of participating in the study. Therefore, the participant or their legally authorized representative should indicate that an appropriate discussion has taken place, and open communication will continue to occur throughout the study.
- Participants who are patients and asked to participate in a diagnostic or therapeutic trial should be notified of any alternative choices for diagnosis or treatment. If the study includes randomized treatment and the use of a placebo, the information needs to be disclosed to the participant and included in the consent form. The person obtaining consent must not withhold any information from the participant that might influence the decision, nor make promises of beneficial results yet to be proven.
- The informed consent process must minimize the possibility of coercion or undue influence.

The Principal Investigator does not have to obtain consent personally. A qualified Co-investigator or other individual listed on the IRB-approved study team list may obtain consent from potential study participants. All persons who will be obtaining consent must have achieved certification in human subject protections (CREC Certification). Individuals obtaining consent must be knowledgeable about the study and capable of answering study-related questions posed by participants.

Informed consent must be obtained under circumstances that give the individual sufficient opportunity to consider whether to participate in the research study, and that minimizes possible coercion or undue influence. This includes providing the participants or their parents, guardians or legally authorized representatives adequate time to read the consent, ask questions, and consider the risks and/or benefits prior to obtaining their signature.

It is the Principal Investigator's responsibility to assure that the informed consent process is an ongoing exchange of information between the research team and the study participant throughout the course of a research study. Informed consent is a continuous process of communication and acknowledgement over time, not just a signed document.

A signed and dated copy of the current IRB-approved informed consent document must be given to the participant or their parent, guardian, or legally authorized representative.

Any revisions to the informed consent process or documents must be submitted as a modification to the IRB. Any newly revised informed consent processes or documents must be approved by the IRB prior to use.

## CHAPTER 11 – The Informed Consent Form

### What Is an Informed Consent Form?

The Informed Consent Document or Informed Consent Form is a formalized, templated document that combines all elements of the informed consent process (see pages 87-90 above) into a singular, reproducible format that is readable and reviewable, as well as providing a dedicated space for attestation. (i.e., provides a space for agreement checkboxes, signatures, and dates/times).

This document may be read to the participant or the participant's parent, guardian, or legally authorized representative; however, the investigator must give either the participant or representative adequate opportunity to read it, ask questions, and select any checkbox options before it is signed and dated ([45 CFR 46.117 \(b\)\(1\)](#)). The participant or the participant's legally authorized representative must sign and date the current, stamped IRB-approved document, and a copy must be given to the person signing the document. For complex studies, CWRU IRB strongly encourages giving the consent document(s) to the potential participant several days in advance of the time they will be asked to sign the consent form. The IRB-approved and stamped informed consent document may be sent via standard mail, fax, or e-mail IF this process has been described in the IRB-approved study protocol (see below, How Can the Use of Fax, Mail, Online Sites, or E-mail be Applied to Document Informed Consent Process?).

The Principal Investigator must retain the original signed informed consent document in their research records for 3 years after the completion of the study or otherwise as designated by the study sponsor.

#### **The Informed Consent Form may be either of the following:**

1. *A Long Form*, which is a written consent document that embodies the basic and required additional elements of informed consent:
  - The investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed.
  - This form may be read to the subject or the subject's legally authorized representative.
  - Whenever the IRB or the sponsor require a witness to the oral presentation, the witness signs and dates the consent document.
  - For participants who cannot read, a witness to the oral presentation signs and dates the consent document. A copy of the signed and dated consent document is to be provided to the subject.
  - The participant or representative signs and dates the consent document.
  - The individual obtaining consent signs and dates the consent document.
  - A copy of the currently approved and IRB date-stamped informed consent documents must be given to the participant or their legally authorized representative. If an unsigned copy is given to the participant it must be an **exact** copy of the signed consent form.
2. *A Short Form*, which is a written consent document stating that the elements of informed consent have been presented orally to the participant or the participant's LAR and that the key required information was presented first to the participant before other information, if any, was provided. **The short form consent process is generally used when the subject is unable to read the long form version of the consent due to a language barrier (see below, What are Procedures to Enroll Non-English Speaking Participants?).** An interpreter is utilized for subjects who are



unable to understand the language in which the long form consent is written. When this method is used:

- The consent document states that the elements of disclosure required by regulations have been presented orally to the participant or the participant’s legally authorized representative.
- A written summary embodies the basic and required additional elements of disclosure.
- There will be a witness to the oral presentation.
- For participants who do not speak English, the witness is conversant in both English and the language of the subject.
- The participant or the participant’s legally authorized representative will sign the consent document.
- The witness will sign both the short form and a copy of the summary.
- The person actually obtaining consent will sign a copy of the summary.
- A copy of the signed short form will be given to the subject or the legally authorized representative.
- A copy of the signed summary will be given to the subject or the legally authorized representative.

## Which Informed Consent Form Should My Study Use?

There are 3 (three) consent templates located in the Library section of SpartaIRB: CWRU Consent Template Biomedical (HRP-506CBIO), CWRU Consent Template SBER (HRP-506SBER), and CWRU \*Consent Template Exempt (HRP-506Exempt Research), as well as 1 (one) CWRU Assent (HRP-506ASSENTC) template. See The type of protocol submitted should correspond to the selected consent template. For example, if your study uses the CWRU Protocol SBER (HRP-503SBER), you should select the consent template CWRU Consent Template SBER (HRP-506SBER). Be sure to select templates with CWRU identified in the document name; do NOT use templates with UH in the name.

Each template contains brief instructions for utilizing the template, as well as partially pre-completed sections which allow the PI and/or PI Proxy to easily enter relevant information. Please note that submitted consent forms may be returned for modifications to secure approval if the forms are incomplete, contain irrelevant sections (e.g., retain the Privacy of Protected Health Information (PHI) section when the study is not subject to the HIPAA Privacy rule), have failed to change all the font color to black, or do not exactly match the information found in the submitted protocol and/or executed funding agreements.

CWRU IRB recommends that, after editing to include study-specific information, the consent and assent templates be saved with a document name that matches the study title or IRB identification number (e.g., STUDY20250000 ICF). This will allow for swift identification by both the IRB and study team members.

### ***What is a Child Assent Form and when do I need to use one?***

According to the regulations set forth in [45 CFR 46](#), “Assent” means a child’s affirmative agreement to participate in research. A minor’s failure to specifically object to or decline participation, without explicit affirmative agreement, can NOT be construed as assent. Therefore, an Assent Form is used to document the minor’s unambiguous agreement to study participation. Note that parental permission will also be required using an Informed Consent Form unless otherwise waived or altered according to the approved study protocol. The assent process should mirror the consent process outlined above in Chapter 10.



Child assent takes into account factors such as age, maturity, and psychological state. Generally, studies should plan for children under the age of 18 (up to the age of 17) to sign an assent form. However, it is recommended that studies with child participants of any age consult with the CWRU IRB ([cwru-irb@case.edu](mailto:cwru-irb@case.edu)) to determine appropriate consent/assent procedures and documentation.

Assent forms should be written in a manner that is appropriate to the reading and comprehension levels of the study population. For instance, adolescents may be able to understand more complex concepts and therefore the assent structure and language may more closely mirror those of an adult consent form. Younger children, however, might not be able to comprehend the full purpose and scope of study procedures, but may be able to understand what the experience, time, and any discomforts will be like. In those instances, the assent language may be supplemented with images or examples that may help the child fully better comprehend the experience of study participation.

For more information regarding child assent, see [Research with Children FAQs | HHS.gov](#) and Chapter 15 – Including Children In Research.

## What Are Procedures to Enroll Non-English Speaking Participants?

An investigator who intends to include non-English speaker individuals must provide sufficient detail in the research protocol regarding the plan for inclusion, including the plan for obtaining informed consent and HIPAA Authorization (if applicable), and additional provisions made during the conduct of the study. Participants who do not speak English must be given an informed consent document written in a language understandable to them.

Translated consent documents for populations that are non-English speaking must be submitted for review and approved by the IRB. The Principal Investigator must provide the qualifications of the individual or the service that was used to translate the informed consent documents. The Principal Investigator may wish to delay translating and submitting the consent documents until IRB has granted approval for the English version.

When informed consent is obtained from non-English speaking participants using a translated consent form all of the following must be done:

- The oral presentation must be approved by the IRB and be provided to participants in the language understandable to them.
- A translator who is familiar with the research study and who is fluent in both English and the language of the participant must be present if the person obtaining consent does not speak the language of the participant. Having children translate for adults is not acceptable.
- The consent document must be signed and dated by the participant, parents, guardians, and/or the participant's legally authorized representative (unless the IRB has waived written consent).
- The consent document must be signed and dated by the person obtaining consent and, if the person obtaining consent does not speak the participant's language, by the translator.

A "short form" informed consent may be approved for use by the IRB. A "short form" consent form is a document that contains a brief paragraph that affirms all the elements of informed consent (as required by the federal Regulations) were reviewed with the participant in a language understandable to the subject. The "short form" must be in the participant's native language.

To allow the use of the short form of consent documentation, the IRB determines:





- The consent document states that the elements of disclosure required by regulations have been presented orally to the subject or the subject's legally authorized representative.
- A written summary embodies the basic and required additional elements of disclosure.
- There will be a witness to the oral presentation.
- For participants who do not speak English, the witness is conversant in both English and the language of the subject.
- The subject or the subject's legally authorized representative will sign the consent document.
- The witness will sign both the short form and a copy of the summary.
- The person actually obtaining consent will sign a copy of the summary.
- A copy of the signed short form will be given to the subject or the legally authorized representative.
- A copy of the signed summary will be given to the subject or the legally authorized representative.

## What Is the Documentation of Consent Checklist?

For studies without a waiver of consent documentation, a checklist documenting the circumstances and outcome of the consent process should be completed and filed in the participant's research record.

Components of the consent checklist may include:

- How and where consent was obtained
- The participant's level of comprehension (did they appear to understand, did they ask questions, were they able to reiterate or verbalize the main purpose of the study, procedures, risks, etc.)
- The participant's decision-making capacity at the time of consent (were they alert and oriented)
- Whether others were involved in the decision-making process
- The time given for the participant to review the consent document, consider the research, and ask questions to their satisfaction;
- Identifying who was present during the consenting process
- Affirming that a copy of informed consent document was provided to participant
- Affirming that the participant signed and dated the ICF before any study procedures were performed

The requirement for documenting the consent process applies to all interventional protocols and any protocol for which additional documentation would be warranted. An example of the Informed Consent Checklist can be found here: [CWRU Informed Consent Checklist Guidance](#)

## How Can the Use of Fax, Mail, Online Sites, or E-mail be Applied to Document Informed Consent Process?

For minimal risk studies (e.g., studies involving questionnaires, surveys), the IRB may approve a process that allows the informed consent document to be given to the potential participant by facsimile, mail, online sites, or e-mail. Original, signed consent forms should be returned by mail. Mail out two (2) sets of consent documents so that participants may keep one set for their own personal records. Unique situations or alternative approaches should be discussed with the IRB.

For greater than minimal risk protocols, generally, using fax, mail, or email to obtain documentation of informed consent is not appropriate. The IRB must be consulted on a case-by-case basis to determine the appropriateness of the process.



## When Should A Participant Be Re-consented?

The IRB requires investigators to re-obtain consent of participants when specific conditions are met and/or when specific situations occur.

If the re-consent process includes a revised consent form for a current IRB-approved protocol, that form must be submitted to the IRB as a protocol modification via the Sparta IRB Electronic System and must be approved by the IRB before implementation. If the changes increase subject risk, the change usually requires approval at a convened IRB meeting.

The IRB does not require a subject to re-consent at the time of the protocol continuation approval, unless there have been modifications to the consent form that would affect an individual subject. Federal regulations do not require re-consenting of participants who have completed their active participation in the study, or of participants who are still actively participating, when the proposed change will not affect their participation.

However, when changes do occur in the conditions or the procedures of a protocol that would affect an individual subject, the investigator should once again seek informed consent from the subject. Those participants who are presently enrolled and actively participating in the study should be informed of the change and re-consented if it might relate to the subject's willingness to continue their participation in the study. Adverse events may occur during a research activity that would directly affect whether prospective or enrolled subject would wish to continue in a particular research activity.

### *What Are Examples of When Re-consent is Required?*

#### **Re-consenting Children Who Become Adults While Participating in a Research Study**

When a child who has been enrolled in a research study reaches 18 years of age, the subject must be re-consented as an adult.

#### **Addition of Risks or Significant Revision to Consent Form**

Enrolled subject must sign a revised consent form if the consent has been significantly revised and/or includes the addition of risks to the subject. The changes from the original consent form should be explained to the subject. If the only change to a consent form is an update to the UHCMC's standard research consent language, re-consent is not required.

#### **Decisionally Impaired Research Participants**

If consent has been obtained from a legally authorized representative, and if the subject regains the capacity to consent, the subject must be re-consented using standard consenting procedures. If the subject refuses consent, any data previously collected cannot be used for research purposes. In protocols where a return to normal cognitive functioning is likely, investigators must include their plan to re-consent the subject, including the time frame. Consent must be obtained as soon as possible, once a subject has regained the capacity to provide consent.

#### **As Part of Compliance Review**

As a consequence of a compliance determination by the IRB, a corrective action may require re-consenting participants before previously collected data can be used for research.



### **When the Principal Investigator is Changed**

Participants who are active in a study must be informed when the PI changes. Re-consent is recommended when active participants are still coming in for study visits, however, in certain situations, it could be appropriate to use a signed notification to document the participant was informed. A copy of this signed notice must still be given. If participants are still active but attending study visits yearly or less frequently, notification may be made by mail. When participants are no longer active, and all study participation is over, notification is not required.

## **What Is a Certificate of Confidentiality (CoC)?**

A Certificate of Confidentiality (CoC) is issued to protect participants' privacy and ensure the confidentiality of their data. The Certificate prevents researchers from having to release identifying information about human research participants in any Federal, State or local civil, criminal, administrative, legislative, or other proceeding, or to any other person not connected with the research. This protection is afforded by the Public Health Service Act 301(d), [42 USC 241\(d\)](#). The law focuses on the identifiability of the information, and not the sensitivity of the information.

Any person engaged or intending to engage in research that will collect identifiable and "sensitive" information about participants should apply for a Certificate. Sensitive identifiable information includes all information that identifies an individual, or for which there is at least a very small risk that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual. Sensitive information specifically consists of includes (but is not restricted to):

- Information regarding the use of alcohol, illegal drugs or other addictive products
- Information concerning illegal behavior
- Information that can be destructive to the subject's financial standing, employability or reputation within the community or might lead to social disgrace or prejudice
- Information regarding the subject's psychological state or mental health
- Genetic information or tissues samples
- Information regarding sexual practices or preferences

### ***When Is a Certificate Issued and What Does it Protect?***

NIH-funded researchers are automatically issued a CoC with their award for any NIH-funded research that collects or uses identifiable, sensitive information that was on-going on or after December 13, 2016. For these projects:

- The CoC is issued as a term and condition of the award
- NIH does not issue a physical certificate

Additionally, other Department of Health and Human Services (HHS) agencies issue CoCs to researchers that they fund. Faculty members not funded by NIH or HHS agencies can continue to apply for CoCs through NIH or FDA, as appropriate.

Researchers planning to collect sensitive information for non-NIH funded studies must apply for a Certificate of Confidentiality. The CWRU HRPP Office ([cwru-irb@case.edu](mailto:cwru-irb@case.edu)) should be contacted for assistance. Once local IRB approval has been obtained, with language in the informed consent document that notes a Certificate of Confidentiality will be obtained for the project, the faculty member can apply for a new Certificate via NIH or other funding agencies website. The NIH online CoC System

is utilized with sign-off from a CWRU Organizational Official to request a new CoC. Once a CoC is obtained, the informed consent document should be modified to contain language that the research is protected by the certificate.

**How do I apply for a Certificate for non-NIH funded studies?**

Applications should be made after the IRB has reviewed and approved the protocol. Certificates of Confidentiality are issued by agencies within the Department of Health and Human Services (such as the Centers for Disease Control and Prevention, Food and Drug Administration, or National Institutes of Health), and researchers should apply to the particular agency involved in the funding or regulation of the study, or to the NIH Institute or Center that funds research in a scientific area similar to your project.

Please contact the Research Compliance Officer, Kim Volarcik (kav6@case.edu) for help with this process and for overall sign-off with the agency.

**How do Certificates apply to multi-center trials?**

For multi-site protocols, the coordinating center of non-NIH funded research may apply for a Certificate to cover all sites. The coordinating institution must have the IRB approvals from all sites available upon request for the NIH. All consent forms from all sites should state the correct language regarding the Certificate.

**What are the IRB requirements relating to Certificates of Confidentiality?**

NIH funded studies that include the collection or use of identifiable, sensitive information must add language to the informed consent document that states that the research is covered by a Certificate of Confidentiality and explain the protections offered by the Certificate, and any limitation to these protections. Suggested text can be found in the CWRU informed consent templates for social behavioral and biomedical research found in the SpartaIRB system Library and Template tabs.

## What Are the Requirements for Posting of Clinical Trial Consent Forms [\[§46.116\(h\)\]](#)?

The Revised Common Rule includes a requirement for the posting of one IRB-approved consent form to a publicly available Federal website for each clinical trial conducted or supported by a Common Rule department or agency after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject. This requirement may be satisfied by either the awardee or the Federal department or agency. If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal website (e.g., confidential commercial information), the department or agency may permit or require redactions to the information posted. For more information see Chapter 26 – Overview of ClinicalTrials.gov Records.



## CHAPTER 12 – Remuneration

### Definitions Pertinent to Remuneration

**Remuneration** is any payment in dollars or items of cash or cash equivalent (i.e., checks or gift cards) given to individuals participating in a study.

- Includes both reimbursement of expenses and payment for time and discomfort.
- Is considered taxable income to the research participants regardless of the dollar amount.

**Reimbursement** refers to payment for expenses incurred by study participants such as parking, transportation, or meals while participating in clinical research. Reimbursement of out-of-pocket expenses related to research based on receipts provided by the research subject is not considered taxable income.

**Tangible Gifts** refers to items of nominal value (typically < \$100 value) that are given to research participants (i.e. toy for a child subject, a tote bag or water bottle).

Research participants may be reasonably remunerated or paid for their time, expenses, inconvenience and for the degree of discomfort they may experience while participating in a research study. However, the remuneration should not be so large as to induce individuals to participate in the research against their better judgment. Payments – whether cash or cash equivalent – may not be of such an amount as to result in coercion or undue influence on the decision to participate or continue participation. Participants may be reimbursed for lost earnings, travel costs and other expenses incurred. All remuneration, reimbursements or in-kind services must be approved by the CWRU IRB.

The IRB will consider the cultural, financial, and educational status of potential participants when determining whether proposed compensation plans are appropriate.

Payment amounts, timing, and method of payment must be described and justified in the protocol. The IRB encourages describing reimbursement of expenses separately from payment for time and discomfort. Payment cannot be viewed as a mechanism to offset research risks in deciding whether a protocol should be approved. Risks that are otherwise unacceptable cannot be made acceptable by offering increasing amounts of money to participants,

### How Is an Appropriate Remuneration for Research Participants Determined?

If a study offers remuneration in exchange for participation in the research study, the remuneration offered is not considered a benefit of research but is for the time and effort devoted to participation in research by individuals. Payment amount, including the timing and method of payment must be specified in the protocol and consent form at the time of initial review. The consent document must list what is being paid for and when and in what manner the participants will be paid, including the total amount the subject will receive and how it will be prorated. The proposed payment schedule must be included in the research protocol and consent form. Any change in the payment to participants must be submitted to the IRB as a change to the protocol with appropriately modified consent/assent forms and other study documents.

Subject payments should generally be made upon completion of each study visit, unless otherwise justified in the research protocol. In certain circumstances it may be acceptable to withhold some or all of the



payment until the end of the study. In these situations, payment or credit for payment must accrue as the study progresses to be paid out once participation is complete. If a subject withdraws from the research study or is discharged from the study any payments that have accrued as a result of participation must be provided promptly unless the application and consent form states otherwise. A small proportion of the study payment may be held and paid as a completion bonus as long as the IRB determines the amount would not coerce the subject staying in the study. The IRB encourages describing reimbursement of expenses separately from payment of time and effort.

## What Should Be Considered for Remuneration in Research Involving Children?

In protocols involving children as participants, the division of payment for time and discomfort between the parent and child must be age appropriate and stated in the protocol and consent/assent forms. It is the recommendation of the IRB that payment for time and discomfort in protocols including children should include age-appropriate payment to the child-participants. Payments should never be so large as to induce a subject to submit to research that they might otherwise reject or to induce parents to keep their child in research to which the child objects.

## What Are the Financial Reporting Requirements?

Tax laws and HIPAA regulations regarding the privacy of personal health information must be followed when the decision is made to provide remuneration to research participants. Participants receiving payment are required to complete an IRS W-9 form. Participants receiving more than \$600 in one calendar year must be informed that a 1099-Misc form, which requires a social security number, will be issued to the Internal Revenue Service. In addition, a copy of the 1099-Misc form will be mailed to the address provided on the W-9 form for tax-filing purposes. The payments they receive are considered taxable income and the following language must be in the consent form, if applicable:

*“To receive payment, you must agree to complete a W-9 form which requires you to provide an address to the accounting department. This payment to you may be considered taxable income by the IRS. You will be issued a 1099-Misc form, which requires a social security number, only if payment exceeds \$600 from all studies in which you are participating in a fiscal year.”*

Records containing social security numbers should be stored securely and separately from the research record. Individuals objecting to completing an IRS W-9 form should be informed that they may not be able to participate in the research study. Individuals inquiring about the option of participating without payment may be informed that this is an acceptable option. The subject’s inquiry and agreed upon plan must be documented in the research record. Investigators will comply with university fiduciary policies.

## What Are CWRU Approved Methods to Compensate Research Participants?

The CWRU Research Participant Payment Guidance ([CWRU Research Participant Payment Guidance Update Rv Dec 2023.pdf \(case.edu\)](#)) can be found in Appendix C. The document provides guidelines and procedures regarding utilization of the various CWRU approved payment methods available to compensate research participants, such as gift cards, petty cash, payment requests, PNC e-Payments, and contactless payment apps. The documents also informs the CWRU Research Community on how to maintain compliance with the University’s tax withholding and reporting obligations, funding agency guidelines, and the approved IRB protocol.



## CHAPTER 13 – Investigational Drugs or Biologics in Research

The use of an Investigational Drug and/or Biologic in research is subject to the United States Code of Federal Regulations [Title 21 - Food & Drugs Part 312](#) - Investigational New Drug Application (IND). This guidance defines the applicability of the Code of Federal Regulations and the procedures the CWRU IRB follows to determine whether an IND is needed for a clinical investigation; outlines the responsibilities of the investigator who holds the IND; and establishes procedures for the proper control, storage, use and handling of investigational drugs.

The CWRU IRB Office and CTSC FDA Guidance Core will work with the investigator and manufacturer to determine the need for an Investigational New Drug Application. The proposed research is not allowed to begin until a valid IND is in effect, or until it has been determined by the IRB that the research meets exemptions from the requirement for an Investigational New Drug Application under [21 CFR 312.2\(b\)](#) . This includes recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND.

In order to verify the validity of the IND, a copy of the letter from the FDA with the IND assignment for the clinical investigation under review, or a letter from the FDA stating that an IND is not needed, is required to be submitted to the IRB with the new protocol application.

When a CWRU investigator is the sponsor of the Investigational New Drug (sponsor-investigator), the CWRU IRB requires the investigator to meet with the CWRU Clinical Translational (CTSC) Core to review their FDA responsibilities as a sponsor-investigator. Documentation of this review is sent to the CWRU IRB with citations in writing that the review has taken place, and that the investigator understands their FDA Investigational New Drug application responsibilities. Approval to initiate the research is contingent upon receipt of written documentation from the CTSC Core.

In accordance with FDA regulations [21 CFR 312.3](#), and [Good Clinical Practice \(GCP\)](#) guidelines, the requirements applicable to a sponsor-investigator under part 312 include both those of an investigator and a sponsor. The responsibilities include the following:

- Maintaining the Investigational New Drug application
- Obtaining qualified Investigators and Monitors
- Providing necessary information and training for Investigators
- Monitoring the investigation
- Controlling the investigational agent
- Reporting Significant Adverse Events to FDA/Investigators
- Maintaining and retaining accurate records
- Implementing and maintaining quality assurance with written Standard Operating Procedures (SOP's)

In accordance with FDA regulations [21 CFR 312.2](#) all clinical investigations that involve drugs for any use other than that of a marketed drug in the course of medical practice must have an Investigational New Drug Application, unless the drug meets one of the exemptions from the requirement for an Investigational New Drug Application in [21 CFR 312.2\(b\)](#). These categories are:

**Exemption #1:**

- The drug is lawfully marketed in the United States.





- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- The investigation is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50.
- The investigation is conducted in compliance with the requirements of [21 CFR 312.7](#).
- The research does not involve an exception from informed consent under [21 CFR 50.24](#).

**Exemption #2:**

- The research involves one of the following in vitro diagnostic biological products:
  - Blood grouping serum;
  - Reagent red blood cells; or
  - Anti-human globulin.
- The in vitro diagnostic biological product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- The in vitro diagnostic biological product is shipped in compliance with [21 CFR 312.160](#).
- The research does not involve an exception from informed consent under [21 CFR 50.24](#).

**Exemption #3:**

- The drug is intended solely for tests in vitro or in laboratory research animals.
- The drug is shipped in compliance with [21 CFR 312.160](#).
- The research does not involve an exception from informed consent under [21 CFR 50.24](#).

**Exemption #4:**

- Use of a placebo.
- The research does not involve an exception from consent under [21 CFR 50.24](#).

## Ordering, Handling, Storage, and Disposition

In accordance with FDA regulations [21 CFR 312](#) and CWRU policies, the Sponsors and/or Investigators are responsible for the proper ordering, handling, storage and disposition of investigational drugs in clinical trials at CWRU. If the Principal Investigator does not delegate this responsibility to an Investigational Drug Service, then the Principal Investigator must complete an Investigational Drug Services Exception request form and ensure the following:

### **1. Prescribing**

- Prescribing an investigational drug must be done by an authorized prescriber listed on the IRB approved protocol. The authorized prescriber must be licensed and be credentialed through their institution.



**2. Procurement**

- Procurement of an investigational drug must be done by the Principal Investigator or designated study personnel according to the terms of the executed agreement and only after the protocol has been approved by the IRB.

**3. Receipt**

- Investigational drugs may only be received by the Principal Investigator or designated study personnel at a CWRU or the designated institution's (where the study is being conducted) business address (the address listed on the 1572).
- Upon receipt of the investigational drug, the Principal Investigator or designee will inventory the shipment to ensure that the information on the packing slip matches exactly with what has been shipped, including lot numbers and quantity.
- Packing slips and documentation of inventory must be maintained with the study records.

**4. Storage/Labeling**

- Investigational drugs used in conjunction with a research protocol must be kept in a locked and secured area and must be labeled "Caution: New Drug-Limited by Federal Law (or United States) Law to Investigational Use."
- Additional labeling for inpatient Investigational Drugs shall be in compliance with CWRU policies. Any other information pertinent to administration of the Investigational Drug may also be included on the label (e.g., expiration date).
- Labeling for outpatient Investigational Drugs must include subject study identification number, date dispensed, prescription number, study drug name, directions for use, the name of the Principal Investigator, the name and address of prescriber and quantity dispensed.
- Access to investigational drugs must be limited to personnel designated by the Principal Investigator.

**5. Dispensing**

- The investigational drug may not be given to anyone not enrolled in the study.
- The Principal Investigator must not supply the investigational drug to any person not authorized.
- Dispensing of the study drug must be done by an authorized prescriber listed on the IRB approved protocol.
- For accountability purposes an investigational drug accountability log(s) must be kept for all investigational drug studies. Documentation of the following elements should be recorded for each drug used:
  - Name of Principal Investigator
  - Name of study drug
  - Protocol title
  - Drug dose, form and strength
  - Expiration date of the drug (if available)
  - Research subject study ID number
  - Date dispensed
  - Quantity dispensed
  - Dose
  - Date returned
  - Quantity returned
  - Balance
  - Lot #



- Signature and/or initials of staff member
  - Personnel may not remove any drug(s) from the standard drug inventory and substitute them for an investigational drug, even if the drug, under study, is approved and used in practice.

**6. *Maintaining a Drug Accountability Log***

- Investigational drug logs must be maintained with the study's regulatory records for the period of time required by the federal regulations or terms of the agreement, whichever is longer.
- The full names, titles/positions, signatures and/or initials of all CWRU personnel responsible for maintaining or documenting in the log(s) must be indicated on either a cover sheet or in the log itself.
- The Principal Investigator or designated study personnel must regularly review the drug logs to ensure that there is an adequate amount of drugs available to conduct the study procedures.
- Drug records must show the receipt, shipment, or other disposition of the investigational drug.
- The disposition of the drug, including dates, quantity, and use by research participants must be recorded.

**7. *Disposition***

- Upon conclusion or termination of the clinical investigation, or by the sponsor's request, the Principal Investigator shall return to the sponsor any remaining supply of the investigational drug or otherwise dispose of the drug as the sponsor directs. The investigational drug should not be disposed of by the Principal Investigator or study personnel without obtaining advance written permission from the sponsor.
- Documentation of why, when, and the personnel involved with disposal is required.



## CHAPTER 14 – Investigational Devices Used in Research

### Definitions Pertinent to Investigational Devices

#### ***Investigational Device***

The US FDA defines an investigational device as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

**Please note:** Software (e.g., software that controls a pacemaker) is considered a device.

#### ***Investigational Device Exemption(s) (IDE)***

An Investigational Device Exemption (IDE) allows the investigational device to be used in a clinical trial in order to collect safety and effectiveness data required to support a Pre-market Approval Application (PMA) or a Pre-market Notification [510(k)] submission to the FDA. An IDE permits a device to be shipped lawfully for purposes of conducting investigations of that device. ([21 CFR 812.1](#)). The FDA assigns each investigational device exemption (IDE) to either category A or B. All clinical investigations of devices must have an approved IDE or be exempt from the IDE regulations ([see 21 CFR 812.2](#)).

#### ***Investigational Device Exemption(s) (IDE) Number***

The FDA assigns a special identifier that corresponds to each device granted an IDE.

#### ***Non-Significant Risk(s)***

The Non-Significant Risk (NSR) category was created to avoid delay and expense where the anticipated risk to human participants did not justify the involvement of the FDA. If the IRB determines that the study is NSR, no submission to or review by the FDA is necessary before starting studies in humans. Note: It is very important to note that the terms “non-significant risk” and “minimal risk” are defined separately and are not synonymous.

#### ***Significant Risk(s)***

A Significant Risk (SR) device study is defined as a study of a device that presents a potential for serious risk to health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise prevents a potential for serious risk to the health, safety, or welfare of a subject. If the Institutional Review Board (IRB) determines the study to be SR, the sponsor must obtain an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA) before proceeding with the study.



### ***Sponsor***

A Sponsor is a person who initiates, but who does not actually conduct, the investigation. That is, the investigational device is administered, dispensed, or used under immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

### ***Sponsor-Investigator***

A Sponsor-Investigator is an individual who both initiates and actually conducts, alone or with others, an investigation. That is, a person under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part includes those of an investigator and those of a sponsor.

In accordance with FDA regulations [21 CFR 812.3](#), and [Good Clinical Practice \(GCP\)](#) guidelines; the requirements applicable to a sponsor-investigator under 21 CFR Part 812 include both those of an investigator and a sponsor. The responsibilities include the following:

- Maintaining the Investigational Device Exemption
- Obtaining qualified Investigators and Monitors
- Providing necessary information and training for Investigators
- Monitoring the investigation
- Controlling the investigational agent
- Reporting Significant Adverse Events to FDA/Investigators
- Maintaining and retaining accurate records
- Implementing and maintaining quality assurance

### ***Transitional Device***

A Transitional Device is a device subject to section 520(l) of the FD&C Act and which FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.

## **Investigational Device Exemptions (IDE) Regulations**

Under FDA regulations [21 CFR 812.2\(a\)](#) all clinical investigations that involve determining the safety or efficacy of a medical device must have an Investigational Device Exemption.

There are two ways that a medical device can have an Investigational Device Exemption:

1. FDA issues an Investigational Device Exemption: A copy of the FDA correspondence with information pertaining to FDA review of the device and the IDE number assigned by the FDA must be provided with the protocol submission for review by the IRB.
  - **The sponsor labels the device in accordance with [21 CFR 812.5](#):**
    - The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
    - The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under Part 50 and documents it, unless documentation is waived by an IRB under §56.109(c).
    - The sponsor complies with the requirements of [21 CFR 812.46](#) with respect to monitoring investigations;



- The sponsor maintains the records required under [21 CFR 812.140\(b\)\(4\)](#) and (5) and makes the reports required under [21 CFR 812.150\(b\)\(1\)-\(3\) and \(5\)-\(10\)](#);
  - The sponsor ensures that participating investigators maintain the records required by 21 CFR [812.140\(a\)\(3\)\(i\)](#) and make the reports required under [21 CFR 812.150\(a\)\(1\)\(2\)\(5\) and \(7\)](#); and
  - The sponsor complies with the prohibitions in [21 CFR 812.7](#) against promotion and other practices.
2. The device meets the requirements or an abbreviated Investigational Device Exemption: Research that meets all of the elements of the following category is considered to have an abbreviated Investigational Device Exemption and does not need an FDA-issued Investigational Device Exemption: [[21 CFR 812.2\(b\)](#)]
- **Abbreviated Investigational Device Exemption [[21 CFR 812.2\(b\)](#)], the device is not a significant risk device:**
    - The device is not a banned device.
    - Is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;
    - Is not purported or represented to be for a use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;
    - Is not 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
    - Does not present a potential for serious risk to the health, safety, or welfare of a subject.

**Seven Categories where research involving a medical device is exempt from the requirement for an Investigational Device Exemption [[21 CFR 812.2\(b\)](#)]:**

**Exemption #1:**

A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

**Exemption #2:**

A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under [subpart E of 21 CFR 807](#) in determining substantial equivalence (i.e., “FDA-approved device”).

**Exemption #3:**

- A device is a diagnostic device.
- The sponsor complies with applicable requirements in [21 CFR 809.10\(c\)](#).
- The testing is noninvasive.
- The testing does not require an invasive sampling procedure that presents significant risk.
- The testing does not by design or intention introduce energy into a subject.
- The testing is not used as a diagnostic procedure without confirmation of the
- Diagnosis by another, medically established diagnostic product or procedure.





**Exemption #4:**

A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.

**Exemption #5:**

A device intended solely for veterinary use.

**Exemption #6:**

A device shipped solely for research on or with laboratory animals and labeled in accordance with [21 CFR 812.5\(c\)](#).

**Exemption #7:**

A custom device as defined in [21 CFR 812.3\(b\)](#), unless the device is being used to determine safety or effectiveness for commercial distribution.

## Significant and Non-Significant Risk

In accordance with FDA requirements, it is the policy of CWRU IRB that a determination of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made prior to consideration of IRB approval of the medical device study. The Significant Risk versus Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

All studies using devices with an Investigational Device Exemption number require Full Board approval. If the IRB determines or concurs with the assessment of the sponsor that a device study involves a Significant Risk, then it would be governed by the Investigational Device Exemption regulations at [21 CFR 812](#). The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:

- A description of the device;
  - Reports of prior investigations conducted with the device;
  - The proposed investigational plan;
  - A description of subject selection criteria;
  - Monitoring procedures; and
  - The sponsor risk assessment and the rationale used to make the sponsor's risk determination.
- The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment.

The IRB determination of the risk status of the device will be indicated in formal IRB minutes and correspondences to the investigator (sent via normal mechanisms), and when applicable, will identify that the IRB determination of risk status differs from that submitted by the investigator/sponsor in the application materials. When required, this determination will also be forwarded to the sponsor.

## Clinical and Translational Science Collaboration (CTSC)

When a CWRU Investigator is the sponsor of the Investigational Device Exemption (sponsor- investigator), the CWRU IRB requires the investigator to meet with the Clinical and Translational Science Collaboration



(CTSC) Core to review their FDA responsibilities as a sponsor- investigator. The investigator is responsible for providing the CWRU IRB with documentation in writing that the review has taken place, and that the investigator understands their FDA Investigational Device Exemption responsibilities.

Approval to initiate the research is contingent upon receipt of written documentation from the CTSC Core.

## Ordering, Handling, Storage, and Disposition

In accordance with FDA regulations 21 CFR 812 and CWRU policies, the sponsors and/or investigators are responsible for the proper ordering, handling, storage and disposition of investigational devices in clinical trials at CWRU or its hospital affiliate.

### **1. Ordering**

- Ordering of an investigational device must be done by the Principal Investigator or designated study personnel according to the terms of the executed agreement and only after the protocol has been approved by the IRB.

### **2. Receipt**

- Investigational devices may only be received by the Principal Investigator or designated study personnel at a CWRU business address.

### **3. Storage/Labeling**

- Investigational devices used in conjunction with a research protocol must be kept in a locked and secured area and must be labeled “Caution: Investigational Device-Limited by Federal Law (or United States) Law to Investigational Use.”
- Access to investigational devices must be limited to the Principal Investigator or designated study personnel.
- Study device supplies must be labeled as investigational by the manufacturer and maintained and stored separately by research personnel.

### **4. Dispensing**

- The investigational device may not be given to anyone not enrolled in the study.
- The Principal Investigator must not supply the investigational device to any person not authorized.
- For accountability purposes an investigational device accountability log(s) must be kept for all investigational device studies. Documentation of the following elements should be recorded for each device used:
  - The type of Device
  - Model Number
  - Serial Number
  - Lot Number (if applicable)
  - Date received
  - Research subject name and CWRU ID number (for internal tracking purposes)
  - Research subject study ID number
  - Date implanted or used
- Personnel may not remove any device(s) from the standard device inventory and substitute them for an investigational device, even if the device, under study, is approved and used in practice.



- If the sponsor provides an investigational device accountability log, research personnel must review the log to determine if the required elements are included on the log. If the log provided by the sponsor does not include all of the required elements, a separate log including those elements must be maintained.

#### **5. *Maintaining Investigational Device Log(s)***

- Investigational device logs must be maintained in the study's regulatory binder for the period of time required by the federal regulations or terms of the agreement, whichever is longer.
- The full names, titles/positions, signatures and/or initials of all CWRU personnel responsible for maintaining or documenting in the log(s) must be indicated on either a cover sheet or in the log itself.
- The Principal Investigator or designated study personnel must regularly review the device logs to ensure that there is an adequate amount of devices or the appropriate type of devices available (sizes, etc.) to conduct the scheduled procedures.

#### **6. *Disposition***

- Upon conclusion or termination of the clinical investigation, or by the sponsor's request, the Principal Investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device(s) as the sponsor directs. Investigational device(s) should not be destroyed by the Principal Investigator or study personnel without obtaining advanced written permission from the sponsor.
- Documentation of why, when and the personnel involved in disposition is required.
- In the event of research software, disposition must include the date the software was reprogrammed or removed from the device(s).

#### **7. *Radioactive Materials***

- **Radioactive Material in a Radiation Delivery Device:** The Principal Investigator is required to obtain approval from the CWRU or hospital affiliate's Radiation Safety Committee (RSC) for all research protocols involving a radioactive device. The Radiation Safety approval process involves designation of an individual with the appropriate training to be the Authorized User Physician.
- **Radiation Generating Equipment:** Contact Radiation Safety regarding new and transferred radiation generating equipment (e.g. x-ray unit). Radiation Safety must be notified at least **3 weeks** prior to delivery. New and transferred radiation safety equipment must be tested and accepted by a Radiation Expert in Radiology or Radiation Oncology, as appropriate, prior to use on a human research subject.

#### **8. *Maintenance and Cleaning***

- All investigational devices must be properly maintained and cleaned.



## CHAPTER 15 – Including Children in Research

*This chapter includes important safeguards for the inclusion of children participants in research*

### Definitions Pertinent to Children Participating in Research

#### ***Assent***

A child's affirmative agreement to participate in research. Failure of a child to object to participation cannot be construed as assent. Assent is a process involving communication with the child. A signature on an assent document is not, by itself, assent.

#### ***Adult***

A person who has 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. Who is an adult may vary depending on the specific treatments or procedures involved in the research and on the jurisdiction (e.g., Ohio) in which the research will be conducted.

#### ***Child***

A person who has not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted. In most US states, a child is someone who is age 17 years old or younger. Other countries may define a child differently. For example, in Taiwan a child is someone who is 19 years old or younger.

#### ***Emancipated Minor***

A person under the legal age of majority who, usually via a court order, has the legal rights of an adult. Situations that qualify a person as an emancipated minor vary from state to state. In Ohio, a person under the legal age of majority becomes an emancipated minor by order of the court. Grounds for emancipation include marriage or service in the armed forces. Documentation of emancipation by court order is required before this doctrine can apply in the research context. In some situations, copies of a court order may be required. Please note, if a minor is a parent and has a child of their own that does NOT mean that they are emancipated. In this case, investigators would have to collect assent from the minor parent and parental consent from that minor's parent/guardian.

#### ***Guardian***

An individual who is legally authorized under applicable state or local law to consent on behalf of a child to general medical care.

#### ***Parent***

Parent generally means a child's biological or adoptive parent. **Foster parents are not authorized to give research consent.**

#### ***Permission or Parental Permission***

The agreement of the parent(s) or legally authorized guardian to the participation of a child in research. This term is often used to emphasize that the parent is not the subject of the research. In this context permission has the same meaning as consent.

## What Are Special Considerations When Enrolling Children in Research Studies?

Research, including chart reviews, that involves children or the use of Protected Health Information (PHI) of children must meet the criteria for approval set forth in [45 CFR 46, Subparts A and D](#), unless the research has been determined to be Exempt from IRB review. Please note that there are restrictions for approving Exempt research involving children.

When children are involved in research, federal regulations require the permission of the parent(s) or guardian before a child can be enrolled in research. A guardian is a person appointed by a court to handle the affairs of a minor child or incompetent adult.

### Please note:

- Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.
- Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

## What Is the Definition of a Guardian?

A guardian can consent on behalf of a child to general medical care; however, a guardian of the *estate only* cannot. In order to provide medical consent, including permission to participate in a clinical trial, the guardian must prove that they were appointed by a court. The guardianship cannot be based on informal agreements by the parents or established by current living arrangements (e.g., a child living with an aunt does not make the aunt legally authorized to consent on behalf of that child to general medical care unless the authorization has been made by a court). Documentation that shows a person is the legal guardian of a person is required.

While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent or refuse participation in a research study. Assent is a child's affirmative agreement to participate in research after an explanation of the study in language the child can understand. Failure to object to participation cannot be construed as assent.

The following guidelines have been established by the IRB to assist investigators who conduct research involving children. Federal regulations require that assent must be sought from children unless the requirement is waived by the IRB or is not required under applicable regulations. Assent must be taken seriously by all investigators who include children as participants of research.

It is a requirement that the investigator propose an assent plan as part of a research protocol that includes children as participants. If the investigator believes that assent is not appropriate for the child population being studied, appropriate justification must be provided in the protocol. Requests for waivers of assent need to be specifically requested and subsequently approved by the IRB.

The investigator must also describe the additional safeguards in place to protect the rights and welfare of the children.

The child should be given an explanation of the proposed research procedures in a vocabulary and language that is appropriate to the child's age, experience, maturity, and medical condition. This explanation should



include a discussion of any discomforts and inconveniences the child may experience if they agree to participate in the study.

If assent is solicited, the investigator must respect the child's decision. If the child is asked for assent and refuses, the child's parent(s) or guardian may not override the child's decision.

To obtain valid written assent, the investigator must use the current IRB approved and stamped assent form. If a child becomes an adult during the course of the study, then the assent expires, and the subject must sign the IRB-approved adult informed consent form for the study.

In general, Ohio law does not permit persons under the legal age of majority to consent to research on their own. An exception may apply, however, in the following instances when Ohio law permits minors to consent to:

- Diagnosis or treatment of venereal disease;
- Diagnosis or treatment of any condition caused by drug or alcohol abuse;
- HIV testing;
- Examination if reported as a victim of sexual abuse; performance or inducement of abortion by court order;
- For certain outpatient mental health services (excluding the use of medication) when the minor is fourteen years of age or older;
- Pregnancy; or
- Contraceptive care.

The IRB shall consult with the University General Counsel's Office for guidance in each case prior to approving a protocol invoking these exceptions.

Parent(s) or a guardian are encouraged be present during the process of obtaining assent, but this is not required. Parent(s) or a guardian are encouraged to be present during the research procedures, especially if a young child will be exposed to significant discomfort or if the child will be required to spend time in an unfamiliar place.

The IRB must determine that adequate provisions are made for soliciting the permission of each child's parent or guardian to the extent required by [§46.116 of Subpart A](#), [§46.406](#) and [46.407](#). The IRB may find that the permission of one parent is sufficient for research to be conducted under [§46.404](#) or [§46.405](#).

If a study lasts for multiple years, assent may need to be re-assessed as the child's cognitive ability matures. Also, if a child enters a study at an age where assent is not required, but during the study the child attains the age where assent is required, assent must be obtained for the child to continue in the study.

## What Are Age Guidelines for Assent?

Since there are many variables involved in research with children (age, maturity, cognitive ability, degree of study benefit to the child, health of the child, etc.), the guidelines listed below may not be applicable to a specific study and the investigator may propose and justify a different plan. This may include more than one of the applicable categories listed below based on the investigator's determination in specific cases (e.g., studies involving children of differing ages). The plan must be fully described in the protocol/research





plan and be approved by the IRB prior to implementation. Also, the IRB has the option to require a different approach.

- ***6 Years of Age or Younger, Verbal or Written Assent Is Usually Not Required***  
Consent is based on the permission of the parent or guardian, and no assent is required. A brief verbal explanation of the research procedure(s) should be provided to the child.
- ***7 Through 13 Years of Age, a Separate Assent Script Is Required***  
In addition to the parents' consent form or parental permission form, a separate assent script is required for the child. It should be in language appropriate for children 9-13 years of age. The assent script should outline what is involved for the child and emphasize the voluntary nature of the study. Depending on the research study, it will usually be one to two pages in length.

The assent process must at a minimum communicate the information in the assent script to the child and the investigator must obtain the child's verbal agreement to participate in the study. The assent process must be fully described and justified in the protocol/research plan. The IRB will make the final determination of the assent process.

- ***14 Through 17 Years of Age, a Consent or Assent Form May Be Used***  
Children 14 through 17 years old may give assent after the information in a written permission/assent form has been communicated to them, and the child's agreement to participate in the study has been provided. The IRB may determine that the child can sign the Informed Consent document that has been signed by the parent(s) or guardian. A separate assent form may also be provided to the child if the investigator or IRB believes it would better describe the information provided to the child about the nature of the study. This would most likely apply in complex studies, or to children with mild cognitive impairment. The plan to obtain and document the assent process must be fully described and justified in the protocol/research plan. The IRB will make the final determination of the assent process.

## How to Obtain Verbal Assent

If the IRB determines that the communication of the assent process must be documented in writing, this can be achieved by the child signing the assent form or the parental permission form. However, when verbal assent is approved by the IRB, the investigator must communicate the information in the approved assent form/script to the child. The investigator may confirm that assent was obtained by signing the paragraph below. Sample wording that can be used is as follows:

*I have discussed this research study with the child, using language which is understandable and appropriate. I believe I have fully informed this subject of the nature of the study and its possible risks and benefits. I believe the subject understood this explanation and assented to participate in this study.*

## How to Request a Waiver of Assent

There are circumstances in which the IRB may determine that assent is not a requirement for children to be enrolled in a research protocol. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate.

***Please note:*** The investigator must specifically justify why obtaining assent is not appropriate in the protocol/research plan.

In determining whether children are capable of assenting, the IRB takes into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each individual child participant, as the IRB deems appropriate.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the participants are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with [45 CFR 46.116](#).

A determination that assent is not a requirement for protocols involving greater than minimal risk must be approved at a convened IRB meeting. The IRB's determinations and protocol-specific findings are documented in the IRB minutes. Waiver approvals are listed on the IRB approval letter. For more information on waivers, see Chapter 10, Pages 94-96.

## When Is an Alteration or Waiver of Parental Permission Permitted?

### ***1. Alteration of Parental Permission***

When parental permission is to be obtained the regulations require that both parents provide permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. However, for certain categories of research, such as research involving minimal risk or greater than minimal risk with the prospect of direct benefit ([45 CFR 46.404](#) or [405](#)), the IRB may, when appropriate, determine that the permission of one parent is sufficient.

### ***2. Waiver of Parental Permission***

Under the federal regulation [45 CFR 46.408\(c\)](#) for HHS funded research, if the IRB determines that a research protocol is designed for conditions or for a child subject population in which parental or guardian permission is not a reasonable requirement to protect the child participants (i.e., neglected or abused children), the research is not subject to FDA regulations, and the waiver is not inconsistent with applicable federal, state, or local laws, then the IRB may waive the consent requirements. However, the investigator must provide an appropriate mechanism for protecting the children who will participate as participants in the research as a substitute. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research participants, and their age, maturity, status, and condition.

## What Are Special Circumstances That Alter Standard Consent or Assent Criteria?

### 1. *Emancipated Minors*

Ohio law provides that persons under the legal age of consent achieve emancipation only by court order. Documentation of emancipation by court order is required before a minor may be recognized as an emancipated minor in the research context.

### 2. *Minors Who Are Parents*

In Ohio, parenthood does not emancipate a minor (although it does in some other states). Consent for treatment procedures on a child of a minor parent must be obtained from the parent or guardian of the minor parent.

### 3. *Parent Conflict of Interest*

Parental permission may sometimes be insufficient to proceed with the research. Therefore, the IRB may consider asking for additional protections for the subject, such as the presence of an independent witness or a court appointed guardian, if applicable, to represent the subject.

### 4. *Child Abuse or Neglect*

In research on child abuse or neglect, there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. In these cases, there must be alternative procedures for protecting the rights and interests of the child asked to participate including, perhaps, the court appointment of special guardians. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research participants, and their age, maturity, status, and condition.

### 5. *Wards of the State*

Research involving children who are wards of the state, or any other agency, institution, or entity (including children in foster placement) must have consent for research given by the agency that has custody of the child. This usually requires the agency to appoint a child advocate with the appropriate background and experience to act in the child's best interests. The inclusion of children who are wards of the state usually requires that the research is:

- Related to their status as wards;
- Conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as participants are not wards; or
- A treatment protocol in which the majority of participants are not wards.

### 6. *Research at Ohio Agencies*

- Ohio's Department of Mental Health has an additional requirement ([Ohio Administrative Code 5122-28-05A \(5\)](#)), "When a community mental health board or agency conducts, participates in, or is the site of research activity with human participants, this research activity shall comply with the following requirements: An overt refusal to participate by either the adult or child subject or the parent or guardian is to be taken as final." If the research involves an agency, the agency director shall also provide consent. If the research involves a community mental health board, the community mental health board director shall also provide consent.

## What Are the Office for Human Research Protections (OHRP) Criteria for Approval of Research That Involves Children?

The following criteria for approval of research are met when research involves children are outlined in 45 CFR 46 Part D:

- **Category 1 (45 CFR 46.404):**
  - No greater than minimal risk to children is presented.
  - Where parental permission is to be obtained, the IRB must declare whether one or both parents must give permission for the child's research participation.
  
- **Category 2 (45 CFR 46.405):**
  - More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being.
  - The risk is justified by the anticipated benefit to the participants.
  - The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
  - Where parental permission is to be obtained, the IRB must declare whether one or both parents must give permission for the child's research participation.
  
- **Category 3 (45 CFR 46.406):**
  - More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject.
  - The risk represents a minor increase over minimal risk.
  - The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
  - The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition.
  - Where parental permission is to be obtained, both parents must give permission unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the care and custody of the child.
  
- **Category 4 (45 CFR 46.407):**
  - Research not otherwise approvable and presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
  - Requires approval by the Secretary of Health and Human Services, as applicable.
  - The federal agency, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determined either:
    - The research fell into categories 1 through 3; or
    - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of



children and the research will be conducted in accordance with sound ethical principles.

- Where parental permission is to be obtained, both parents must give permission unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the care and custody of the child.

## CHAPTER 16 – Pregnant Women and Neonates

*This chapter includes important safeguards for the inclusion of pregnant women and neonate participants in research.*

### Definitions Pertinent to Recruiting Pregnant Women as Research Participants

**Pregnancy** encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

**Fetus** means the product of conception from implantation until delivery.

**Neonate** means a newborn. Investigators must submit their study to a hospital IRB such as University Hospitals of Cleveland. Non-biomedical protocols involving neonates may be reviewed by the CWRU IRB.

### What Are Special Considerations When Recruiting Pregnant Women and Fetuses?

A research protocol is considered to include pregnant women, human fetuses, and/or neonates when:

- Any of the above are target populations about which data are collected; or
- Pregnancy occurs during the course of a research study and information about the pregnancy, fetus and/or neonate will be obtained as part of the research study.

The IRB recognizes the additional protections required under federal law for pregnant women, human fetuses and neonates who participate in research ([Subpart B - Additional Protections for Pregnant Women, Human | HHS.gov](#)).

- The CWRU IRB does not review or approve biomedical protocols involving fetuses or neonates.
- Investigators must submit their study to a hospital IRB such as one of CWRU's affiliated hospitals.

### What Are the Required Protections When Recruiting Pregnant Women and Fetuses?

In order to approve the inclusion of pregnant women in a research protocol, the following conditions listed in [45 CFR 46.204, Subpart B](#) must be met (please keep in mind that the following conditions apply most often in biomedical research and do not fall under the purview of the CWRU IRB).

- Where scientifically appropriate, preclinical studies, including studies on pregnant animals and clinical studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- The risk to the fetus:
  - Is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or,
  - If there is no prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important scientific knowledge which cannot be obtained by any other means.
- Any risk is the least possible for achieving the objectives of the research.





- When research involves pregnant women, the IRB determines that the consent of the pregnant women is required if the research:
  - Holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit to the woman or the fetus; or
  - No prospect of benefit for the woman nor fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important knowledge that cannot be obtained by any other means.
- If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father must be obtained in accord with the informed provisions of [45 CFR 46 Subpart A](#), except that the father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
- For children who are pregnant, assent must be obtained from the pregnant child and consent from their parent(s) or legal guardian(s). Please see Chapter 15 and Additional Considerations below.
- No inducement, monetary or otherwise will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in determining the viability of a neonate.

The research protocol must address how these conditions are met and provide sufficient justification for inclusion of pregnant women.

If a research protocol proposes to collect information from the pregnant partner of a research subject, the pregnant partner becomes a “research subject” and the provisions under OHRP regulations, including [45 CFR 46 Subpart B](#), are applicable. This includes obtaining informed consent from the pregnant partner for participation.

## What Are Additional Considerations When Recruiting a Pregnant Participant Who is a Child?

In addition to the regulations under [45 CFR 46 Subpart B](#), if the pregnant subject is also a child, there are additional considerations that must be accounted for under [45 CFR 46 Subpart D](#), Additional Protections for Children Involved as Research Participants.

Prior to inclusion of pregnant children in research, parental permission must be obtained, or the IRB must approve a waiver of the requirement for parental permission in accordance with [45 CFR 46.116](#) or [45 CFR 46.117](#).

In research protocols that involve pregnancy testing of participants who are under the age of 18, the following is required:

- If the female is age 13 years or younger, positive results of the pregnancy test must be shared with both the child and the parent or legal guardian. In addition, the pregnancy must be reported to the local public children’s service agency. This must be documented in the research record.
- If the female is age 14 years or older, the results of the pregnancy test must be shared with the child. The results do not automatically have to be shared with the parent or legal guardian unless the parent or legal guardian asks for the results. This must be documented in the research record.



## CHAPTER 17 – Prisoners as Research Participants

This chapter includes important safeguards for the inclusion of prisoners as research participants.

### Definitions Pertinent to Involving Prisoners as Research Participants

**Prisoner** is “any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing.”

**Interment** in a facility for psychiatric illness or substance abuse is considered to meet the criteria for incarceration if the commitment has been made as an alternative to a criminal prosecution or incarceration. However, an individual in mental health or substance abuse facility is not considered incarcerated if they have voluntarily committed him/herself or has been civilly committed.

**Probationers and parolees** – who are not incarcerated – are not classified as prisoners even though they are under criminal justice supervision. Probation and parole are not considered incarceration.

**Minimal Risk for Prisoners** is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examinations of healthy persons.

### What Are Ethical Considerations When Recruiting Research Participants Who Are Prisoners?

The inclusion of individuals in a research protocol who are considered “prisoners” requires special ethical considerations and additional regulatory requirements to safeguard their interests and protect them from harm. Prisoners constitute a research population who are at risk for coercion due to their legal status or confinement. Prisoners may be under constraints because of their incarceration, which could affect the ability to make a truly voluntary decision with respect to participation as participants in research.

A research protocol is considered to include prisoners when:

- Prisoners are the target population that will be recruited; or
- Participant is a prisoner at the time of enrollment; or
- A currently enrolled participant becomes incarcerated during the course of the study.

When a research protocol involves the inclusion of prisoners, the IRB will review the research in accordance with institutional procedures, as well as in accordance with OHRP regulations as well as with [45 CFR 46 Subpart C](#) (additional protections pertaining to research involving prisoners). Additional rules as determined by federal, state, county, and local regulations may also apply. When a prisoner is a child (e.g., an adolescent detained in a juvenile detention facility is a prisoner), the IRB procedures regarding enrollment of children, [45 CFR 46 Subpart D](#) will be applied.

Federal regulations allow for certain categories of research involving prisoners to be reviewed via expedited procedures. The IRB Office, IRB Chair, and/or Vice Chair will determine if a protocol involving



prisoners can be reviewed via expedited review or if it is required to be reviewed at a convened IRB meeting. If a protocol involving prisoners is designated for expedited review, the IRB prisoner representative member will be assigned as the primary or secondary reviewer.

None of the exemption categories in the HHS regulations for research involving human participants in [45 CFR 46.101\(b\)](#) apply to research involving prisoners for FDA or Department of Justice regulated research. However, research aimed at involving a broader subject population that only incidentally includes prisoners. [[§46.104\(b\)\(2\)](#)] can be exempted.

When research is conducted within the Bureau of Prisons, implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

### ***1. Additional Requirements for New Protocols Recruiting Prisoners as Participants***

**Prisoner Checklist:** To document the above requirements have been met, investigators must complete and a reviewer checklist that includes prisoner requirements via SpartaIRB.

**Research Protocol:** In addition to the standard research protocol requirements, a protocol involving prisoners must clearly articulate that it meets all applicable criteria under [45 CFR 46 Subpart C](#). The protocol must state the following:

- a. Clarification about how the proposed research represents one of the following categories of research permissible for inclusion of prisoners ([45 CFR 46.306\(a\)\(2\)](#)):
  - A study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.
  - A study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.
  - Research on conditions particularly affecting prisoners as a class (e.g., vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of DHHS (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics and published notice, in the *Federal Register*, of his intent to approve such research.
  - Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary of DHHS (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics and published notice, in the *Federal Register*, of his intent to approve such research.
  - Epidemiologic studies that meet the following criteria:
    - The sole purpose(s) are one of the following:
      - To describe the prevalence or incidence of a disease by identifying all cases.
      - To study potential risk factor associations for a disease.
    - The research presents no more than minimal risk and no more than inconvenience to the prisoner-participants, and;
    - Prisoners are not a particular focus of the research.



- b. Discussion about any possible advantages accruing to the prisoner through their participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison. There must also be a confirmation that these advantages are not of such a magnitude that the prisoner's ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prisoner is impaired.
- c. Discussion about the risks involved in the research and justification about how the risks are commensurate with risks that would be accepted by non-prisoner volunteers.
- d. Details regarding procedures for selection of prisoners, including justification for selection procedures to ensure that selection is fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. If a control population is needed, controls must be selected from the group of available prisoners who meet the characteristics needed for that particular research project, unless the Principal Investigator provides to the IRB justification in writing for following some other procedures.
- e. Discussion of the process for obtaining informed consent and study procedures to ensure that the information is presented in language that is understandable to the subject population.
- f. Adequate assurance in the protocol to affirm that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and that each prisoner is clearly informed in advance that participation in the research will have no effect on their parole.
- g. If the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision must also be made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Informed Consent: The informed consent document as well as any study materials must be presented in a language that is understandable to the subject population. The consent form must also clearly address any risks of participation, the voluntary nature of participation, and state that participation in the research will not have any effect on a prisoner's parole.

In certain limited circumstances, informed consent may be waived or altered by an IRB according to 45 [CFR 46.116](#). However, even if informed consent is waived or altered, subpart C of 45 CFR part 46 still requires that the participants be clearly informed in advance that participation in the research will have no effect on their parole, if such notification is relevant.

## **2. *Additional Requirements if a Research Subject Becomes a Prisoner***

If a subject becomes a prisoner after enrolling in a research study, the investigator is responsible for immediately reporting the event in writing to the IRB on an "Unanticipated Problem/Protocol Deviation" form. (NOTE: This is not required if the study was previously approved by the IRB for prisoner participation.) The investigator should provide detail on the subject and the incarceration, as well as the extent of the subject's participation in the research trial up to becoming a prisoner, what remaining study activities the subject has to complete and the plan for either inclusion or exclusion of the subject from further research activities.

If the study was not previously reviewed and approved by the IRB in accordance with the requirements of 45 CFR 46 Subpart C, all research interactions and interventions with, and obtaining identifiable private information from the prisoner must cease until the requirements of Subpart C are satisfied. This is necessary because it is unlikely that initial IRB review of the research and the informed consent documents contemplated the constraints imposed by the possible future incarceration of the subject. If the investigators would like the subject to continue in participation in the research, a modification must



be submitted with revisions to the protocol and consent form to detail how continuation of the prisoner meets applicable criteria under 45 CFR 46 Subpart C (*see section A: “Additional Requirements for New Protocols Enrolling Prisoners as Participants” above*).

The convened IRB will review the current research protocol in which the subject is enrolled, taking into special consideration the additional ethical and regulatory concerns for a prisoner involved in research as per Section C of this guidance “Additional IRB Requirements” noted below.

In special circumstances in which the investigator asserts that it is in the best interest of the subject to remain in the research study while incarcerated, the subject may continue to participate in the research until the requirements of subpart C are satisfied. The investigator must promptly notify the IRB of this occurrence, so that the IRB can re-review the study. Note that in these circumstances, some of the findings required by [45 CFR 46.305\(a\)](#) may not be applicable; for example, the finding required under 45 CFR 46.305(a)(4) regarding the selection of participants within the prison may not be applicable, if the subject was recruited outside of an incarcerated context. The IRB should document findings of non-applicability accordingly.

If research interactions and interventions or obtaining identifiable private information will not occur during the incarceration, IRB review and approval under the prisoner rules is not required.

### **3. *Additional IRB Requirements***

For all new protocols that proposed to recruit prisoners as research participants, or propose to include individuals who subsequently become incarcerated during the course of an active research trial, the IRB will review the protocols to determine if the inclusion is appropriate in accordance with OHRP 45 CFR 46 Subpart C.

In order to review research involving prisoners, the IRB will note appropriate constitution ([45 CFR 46.304 \(a\) and \(b\)](#)) by affirming the following:

- a. A majority of the IRB (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB.
- b. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that, where a particular research project is reviewed by more than one IRB, then only one IRB needs to satisfy this requirement. If a prisoner representative is selected to serve on the IRB, the person must have a close working knowledge, understanding and appreciation of prison conditions from the perspective of a prisoner. Suitable individuals could include present or former prisoners; prison chaplains; prison psychologists, prison social workers, or other prison service providers; persons who have conducted advocacy for the rights of prisoners; or any individuals who are qualified to represent the rights and welfare of prisoners by virtue of appropriate background and experience.

The IRB will meet the special composition requirements for all types of review for the protocol: initial review, continuing review, review of protocol modifications, review of reports of adverse events or unanticipated problems involving risk to participants or others, or in the event an individual becomes a prisoner while participating in a research protocol.

The IRB must also find that the proposed research meets the requirements of [45 CFR 46.305](#), including that the research represents one of the categories of permissible research under [45 CFR 46.306](#). OHRP notes that in order to make some of these seven findings and meet the requirements of subpart A of 45





CFR part 46, the IRB must be familiar with the specific conditions in the local prison(s) or jail site(s) that are pertinent to subject protections, before approving the proposal for the local site (45 CFR 46.107(a)).

In order to approve research involving prisoners, the IRB must find that the proposed research falls into one of the permissible categories of research ([45 CFR 46.306](#)) and make six other findings under [45 CFR 46.305](#). The meeting minutes must document the IRB's discussion of these elements and affirm that the research meets the regulatory criteria. Additionally, the minutes must reference that a majority of the IRB (exclusive of prisoner member/representative) has no association with the prison(s) involved and a qualified prisoner representative was present and voted on the protocol.

#### **4. *Prisoner Certification Letter to OHRP***

An institution that intends to conduct research supported by the U.S. Department of Health and Human Services (DHHS) that will involve prisoners as participants must certify to the Secretary (through [OHRP](#)) that the IRB has made the seven findings required under [45 CFR 46.305\(a\)](#), including the finding that the proposed research represents one of the permissible categories of research under [45 CFR 46.306\(a\)\(2\)](#).

The institution must send OHRP a certification letter, to that effect, which should include the name and address of the institution and specific identification of the research protocol, including the relevant grant number. For DHHS-funded research, the Research Compliance Officer certifies to OHRP the duties of the IRB have been fulfilled.

The OHRP requires the responsible institution to submit a copy of the research proposal so OHRP can determine whether the proposed research involves one of the categories of research permissible under [45 CFR 46.306\(a\)\(2\)](#), and if so, which one. This will include:

- The IRB-approved protocol.
- Any relevant DHHS grant application or proposal.
- Any IRB application forms required by the IRB.
- Any other information requested or required by the IRB to be considered during initial IRB review.

The IRB will also include the following information in its certification letter to OHRP to facilitate processing:

- OHRP Assurance number.
- IRB registration number.
- Date(s) of IRB Meeting(s) in which protocol was considered, including a brief chronology that encompasses the date of initial IRB review and date of Subpart C review.

#### **5. *Other Approvals That May Be Required***

There may be other approvals required depending on the policies and procedures for the correctional facility at which the research will take place (e.g., Federal Bureau of Prisons, Ohio Department of Rehabilitation and Corrections, County Jail, etc.). It is the Principal Investigator's responsibility to determine what additional requirements must be met prior to conducting research that involves prisoners.





**6. *Research Conducted Within the Bureau of Prisons***

- a. The organization, IRB, and researchers and research staff must follow the requirements of [28 CFR 512](#), including:
  - The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
  - The research design must be compatible with both the operation of prison facilities and protection of human participants. The researcher must observe the rules of the institution or office in which the research is conducted.
  - Any researcher who is a non-employee of the Bureau must sign a statement in which the researcher agrees to adhere to the provisions of [28 CFR 512](#).
  - All research proposals will be reviewed by the Bureau Research Review Board.
- b. The researcher must have academic preparation or experience in the area of study of the proposed research.
- c. The project must have an adequate research design and contribute to the advancement of knowledge about corrections.
- d. When submitting a research proposal, the applicant shall provide the following information:
  - A summary statement which includes:
    - Names and current affiliations of the researchers.
    - Title of the study.
    - Purpose of the study.
    - Location of the study.
    - Methods to be employed.
    - Anticipated results.
    - Duration of the study.
    - Number of participants (staff or inmates) required, and amount of time required from each.
    - Indication of risk or discomfort involved as a result of participation.
  - A comprehensive statement which includes:
    - Review of related literature.
    - Detailed description of the research method.
    - Significance of anticipated results and their contribution to the advancement of knowledge.
    - Specific resources required from the Bureau of Prisons.
    - Description of all possible risks, discomforts, and benefits to individual participants or a class of participants, and a discussion of the likelihood that the risks and discomforts will actually occur.
    - Description of steps taken to minimize any risks.
  - A description of physical or administrative procedures to be followed to:
    - Ensure the security of any individually identifiable data that are being collected for the study.
    - Destroy research records or remove individual identifiers from those records when the research has been completed.
  - A description of any anticipated effects of the research study on organizational programs and operations.
  - Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
  - A statement regarding assurances and certification required by [28 CFR 46](#), if applicable.



- e. The research design shall take into account:
  - The selection of participants within any one organization must be equitable.
  - Incentives may not be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the test setting may be offered.
  - Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both:
    - No longer in Bureau of Prisons custody, and;
    - Participating in authorized research being conducted by Bureau employees or contractors.
- f. The informed consent form shall include the required elements of disclosure:
  - Identification of the researchers.
  - Anticipated uses of the results of the research.
  - A statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
  - A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization.
  - A statement that participation in the research project will have no effect on the inmate participant's release date or parole eligibility.
- g. The research design shall maintain the confidentiality of data by the following steps:
  - A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as statistical research or reporting record is provided to the agency.
  - Except as noted in the consent statement to the participant, the researcher must not provide research information that identifies a participant to any person without that participant's prior written consent to release the information. For an additional layer of protection, an investigator should obtain a Certificate of Confidentiality. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.
  - Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
  - If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may be asked to provide ORE with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.
- h. After the protocol is approved by the CWRU IRB:
  - The researcher must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor to the researcher.
  - At least once a year, the researcher shall provide the Chief, Office of Research and Evaluation (ORE), with a report on the progress of the research.



- At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
- In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
- The researcher shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
- Prior to submitting for publication, the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.



## CHAPTER 18 – Decisionally Impaired Persons

*This chapter includes important safeguards for the inclusion of decisionally impaired participants in research*

### Definitions Pertinent to Recruitment of Decisionally Impaired Persons

**Assent** means a subject's affirmative agreement to participate in research. Failure of a person to object to participation cannot be construed as assent. Assent is a process involving communication with the person. A signature on an assent document is not, by itself, assent.

**Cognitively Impaired** refers to an adult with any psychiatric disorder (e.g., schizophrenia, major depression, psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g., dementia), a developmental disorder (e.g., mental retardation, autism spectrum disorder), or severe acute illnesses associated with cognitive impairment (e.g., stroke, seizure, metabolic coma, severe pain) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Depending on the illness the impairment may be temporary, cyclical, or permanent.

**Competence** is a legal term, not a medical term, used to denote capacity to act on one's own behalf, the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice.

**Decision-Making Capacity** refers to a potential subject's ability to make a meaningful decision about whether or not to participate. It is generally thought to include at least the following four elements:

- **Understanding:** the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, as well as the risks and benefits of participating versus not participating.
- **Appreciation:** the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one's own situation and condition.
- **Reasoning:** the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives.
- **Choice:** the ability to understand the difference between participating and not participating in research.

Decision-making capacity is different from the legal concept of competence.

- Incompetence is a legal determination made by a court of law.
- While a court may consider information about a potential subject's decision-making capacity in making a competency determination, the terms are not synonymous.
- For example, someone who is judged legally incompetent to handle their financial affairs may retain sufficient decision-making capacity to make meaningful choices about participating in a particular research protocol.
- Decision-making capacity is situation and protocol specific. Thus, a subject may have capacity to consent to a low-risk research protocol that is not difficult to understand, but not have the capacity to consent to a complex or high-risk protocol.

**Decisional Impairment** refers to a limitation or incapacity that is not part of normal growth and development.



**Guardian** is an individual who is legally authorized under applicable state or local law to consent on behalf of an individual to general medical care.

**Incompetence** is a legal term meaning inability to manage one's own affairs. The term refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incapacity.

**Legally Authorized Representative** means an individual, judicial or other entity authorized under applicable law to consent (provide permission) on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

- While authorizing intervention or research participation for another person is more accurately described as “giving permission,” to be consistent with federal regulations this guidance will refer to this as “consent.”
- The term legally authorized representative may include a person properly appointed by an advanced directive (such as a living will or declaration) or a durable power of attorney for health care, certain court appointed guardians, and next of kin identified below in certain circumstances.
- Documentation of a person's status as a legally authorized representative for a research subject is required and must be carefully evaluated to determine the validity of the appointment and scope, if any, of authority granted to make decisions regarding procedures involved in the research.
- For example, the existence of a durable power of attorney for health care or advance directive for health care may not create a legally authorized representative for any or certain kinds of research decisions.
- The University's General Counsel's Office shall be consulted by the IRB and investigator if there are any questions related to legally authorized representative consent.

## What Are Special Considerations When Recruiting People Who Are Decisionally Impaired?

Disorders and illnesses causing impaired decision-making capacity in adults are a considerable health problem in the United States. These include Alzheimer's Disease, Autism Spectrum Disorder, Fragile X, psychiatric disorders, chronic alcoholism, and AIDS dementia complex. There are also acute illnesses that are associated with impaired decision-making capacity, such as seizures and stroke. Conducting research with and including these populations is extremely important. However, these and other disorders may compromise or eliminate a potential research participant's ability to give legally effective informed consent to participate in research. Institutions and investigators conducting research on decisionally impaired participants must balance the societal commitment to advance important scientific knowledge with the ethical obligation to protect the rights and welfare of human research participants. For these reasons, special protections must be considered by the IRB when reviewing research involving participants with impaired decision-making capacity. Therefore, the Principal Investigator, in concert with the IRB, is responsible for providing specific additional safeguards appropriate to the research study. However, few regulations or guidance documents specifically address research-involving adults who have impaired decision-making capacity. The IRB has developed these guidelines to assist investigators in addressing this issue. These guidelines also align with GCP training.



## ***What Are Important Protections to Include When Recruiting People who are Decisionally Impaired?***

### ***1. Fundamental Principles***

For studies proposing to include adult participants with impaired decision-making capacity the following principles always apply:

- Decisionally impaired participants must comprise the only appropriate population and the research question must focus on an issue unique to this subject population. If the research question can be answered using non impaired participants, then participants with impaired decision making capacity cannot be studied.
- If the research involves greater than minimal risk, the risk must be commensurate with the degree of potential benefit to the individual subject.

### ***2. Problems of Consent and Competence***

Because decision-making capacity is task specific, some decisionally impaired individuals remain capable of making informed decisions for themselves regarding research participation. The capacity to obtain informed consent should be assessed in each individual, for each research protocol being considered. The determination of cognitive impairment does not automatically confer decisional incapacity on affected individuals. Especially in the earliest stages of cognitive impairment, many people with cognitive impairment remain capable of making a wide variety of decisions, including deciding whether or not to participate in research. Identification of these individuals is important both because they should be the highest priority participants for enrolling in studies (if they meet other inclusion criteria), and because they may be able to provide guidance for research decision making for future projects when they may no longer retain decision-making capacity.

Procedures should be developed to enhance the possibility that participants can consent for themselves. The setting in which consent is sought and the person seeking consent should be conducive to promoting a potential subject's ability to comprehend and appreciate what is being asked. Because there are no generally accepted criteria for determining competence to consent to research, the investigator must propose criteria for assessing potential participants, and the criteria must be reviewed by the IRB. Criteria for determining competence vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gains can be anticipated.

There have been several approaches proposed to assess a subject's ability to give informed consent. Whatever approach is taken it is essential to document the plan in detail in the research study protocol. Examples may include:

- A screening standard mental status examination, such as the MINI-Mental Status Exam (MMSE). A MMSE score less than 24 suggests impaired cognitive ability and would require further assessment of the potential research subject's decision-making capacity, or exclusion of that subject from the research.
- The development of a decision-making capacity assessment tool that is specific for the research project.
- A post-consent quiz documenting the participants' knowledge of critical elements in the informed consent form (i.e., nature of the illness being studied, voluntary nature of participation, ability to withdraw at any time, consequences of withdrawing, possible risks and benefits of participation, procedures involved, time required, confidentiality, and whom to call with any questions).





- The study investigators may ask a physician/psychologist outside the research team to evaluate the potential subject's decision-making capacity.

**3. *Risk With No Direct Benefit***

Research protocols that do not hold out a reasonable prospect of direct benefit to the participating participants, and that expose participants to more than a minor increase over minimal risk, should be offered only to those participants who either retain decision making capacity or those who have indicated in an advance directive that they would be willing to be enrolled in such studies. Guardian or next of kin consent is rarely appropriate in these situations.

**4. *Limiting Risks***

Investigators must include in the protocol a description of appropriate psychological or medical screening criteria to prevent or reduce the chances of adverse reactions to research. Investigators may need to be consulted to ensure that proposed research procedures will not be detrimental to the subject's non-research program or treatment plan. Consideration should also be given to the effects of separation from supportive family or friends, which may be a significant risk for this population.

**5. *Assent***

Despite the fact that consent may be obtained from a legally authorized representative, the feelings and expressed wishes of an incompetent subject should still be respected. Participation in research is essentially an optional activity and even an uninformed or uncomprehending refusal should be respected. In the case of research involving more than minimal risk, the objection of an adult subject with limited decision-making capacity to provide assent should be binding, except in rare cases when the IRB makes and specifically documents that the intervention is expected to provide a direct health benefit to the subject and the intervention is available only in the context of the research.

**6. *Temporary Decisional Impairment***

This applies to individuals who have acute cognitive impairment with the expectation of recovery, as well as to individuals with chronic cognitive impairment. In addition to individuals with seizures, strokes, myocardial infarction, encephalitis, etc., acute cognitive impairment also includes individuals who have normal brain functioning but are unable to make research decisions due to severe pain, severe duress, or effects of medication. This situation may occur in protocols doing research in nursing care facilities and/or group homes. Individuals with temporary cognitive impairment rarely have advanced directives or guardians, so next of kin consent may be appropriate in some instances. As soon as research participants regain the ability to consent, their consent must be obtained. If the subject refuses consent, then any data collected must not be used for research.

**7. *Institutionalized Participants***

Research involving persons with impaired decision-making capacity, and who have restraints on their personal freedom due to residence in an institution, need additional protections. An institutional setting can be advantageous to the conduct of research because the population is easily accessible, under close supervision to prevent extraneous influences, and medical monitoring is available. However, persons who are totally dependent on an institution may be vulnerable to perceived or actual pressures to conform to institutional wishes for fear of being denied services or privileges. Also, with little or no opportunity to make decisions regarding their daily living, the ability of institutionalized participants to make choices may be further diminished.

## What Considerations Should Be Taken for Legal Authorized Representatives (LAR) and Research Consent?

1. Investigators must provide potential legally authorized representatives the same information that would be given to potential research participants. If there are ongoing decisions during the study regarding the subject's participation or changes to the study, the legally authorized representative must be willing to remain involved in the decision-making process. Investigators must clearly describe the consent process in the protocol/research plan, including how the consent process will be documented.
2. If the subject's condition or other factors change, then the legally authorized representative retains the right to decline enrollment or withdraw the subject from a study if they determine that study participation would either not be in the subject's best interests or would not be consistent with what the subject intended, even if the decision would conflict with the subject's advance directive.
3. If the legally authorized representative's consent has been obtained and if the subject regains decision-making capacity to consent, then the subject must be consented using standard consenting procedures. The process of obtaining consent should be documented in the subject's study records. If the subject refuses consent, any data previously collected cannot be used for research purposes. In protocols where a return to normal cognitive functioning is likely, investigators need to have a plan that includes consenting the participants as soon as possible.
4. Legally authorized representatives are prohibited from receiving any remuneration for providing consent. This does not prohibit the legally authorized representative from being compensated for time and reasonable expenses they incur if they are a study subject.
5. When reviewing research involving individuals who are determined to be decisionally impaired and/or lack decision making capacity and for which there is no authorized guardian or advance directive, the IRB must find and document in the minutes that the use of a legally authorized representative is appropriate and that the legally authorized representative consent process was reviewed and approved for such use. The IRB must also determine that the research objective is important and that there is no way to accomplish the research objective in a population that is not decisionally impaired.

## What Should Be Taken Into Consideration for “Next-of-Kin” (NOK) and Research Consent?

1. In the absence of a court appointed guardian or advance directives speaking directly to research decision making, health professionals offering research enrollment to individuals who are deemed by a court to be incompetent or who lack decision making capacity may consider obtaining consent from qualified next-of-kin in instances when **specifically approved by the IRB**.
2. Consent by the subject's next-of-kin may be obtained from any of the following potential persons who have reasonable knowledge of the subject, in the following descending order of priority:
  - The spouse of the subject.
  - An adult child of the subject or if there is more than one adult child, a majority of the subject's children who are available within a reasonable period of time for such consultation.
  - A custodial parent of the subject.



- Any adult sibling of the subject or if there is more than one adult sibling, a majority of the subject's siblings who are available within a reasonable period of time for such consultation.
  - The nearest adult who is related to the subject by blood or adoption, and who is available within a reasonable period of time for such consultation.
3. A major consideration in evaluating next-of-kin is that they know the subject well enough to be able to make the decisions concerning research participation that the subject would make if they were able to do so. It should be kept in mind that next-of-kin may be subject to conflicting interests because of financial pressures, emotional attachments, or other feelings common in such close relationships. Characteristics to consider include:
- Does the NOK have reasonable knowledge of the subject?
  - Is the NOK familiar with the subject's degree of impairment?
  - Does the NOK have knowledge of the subject's wishes and value system?
  - Is the NOK willing to serve as the substitute decision-maker?
  - Does the NOK understand the risks, potential benefits, procedures and available alternatives to participation in the research protocol?
  - Can the NOK make decisions based on the subject's known preferences and, where the subject's preferences are unknown, make decisions based upon judgment of what the subject's preferences would be even if they are different from the NOK's preferences?
  - Is the NOK willing to remain involved in speaking for the subject until the study is complete or until the subject can speak for themselves?
4. If there is more than one next-of-kin who qualifies to provide consent (e.g., several adult children), it is important that all are in agreement before the subject is enrolled in the research.
5. Proposed protocols should include provisions for next-of-kin to document in the research records a willingness to serve as the substitute decision-maker, the relationship to the subject, and factors to demonstrate reasonable knowledge of the subject's condition and preferences. The University General Counsel's Office is available for consultation relating to guardianship in appropriate cases.

## What Are Approaches to Include Participants Who Possibly Have Impaired Decision-Making Capacity?

1. The initial evaluation is always whether the subject is capable of giving consent. In most studies, participants with impaired ability to give consent are ineligible for the study. For protocols addressing issues in cognitively impaired individuals, the answer may be clear based on the study design. For example, most dementia-affected elderly participants might be decisionally impaired. For other protocols, the answer may need to be determined for each potential subject. For example, in a study of patients with mild to moderate Alzheimer's disease, some participants may be capable of giving consent and others may not. The complexity and risk level of the protocol is also important in this decision. A potential subject could have sufficient decision-making capacity to consent to a simple minimal risk protocol, but not have the capacity to understand a complex or high-risk study. Every effort must be made to maximize the factors that would promote the ability of the subject to give consent. In instances when it is likely that the subject's capacity may become impaired over time, efforts should be made at the outset to identify the process for consent, assent, and guardian and/or legally authorized representative consent (i.e., for longitudinal studies, it is important to re-consent participants with fluctuating or diminishing capacity for consent).



2. If the subject is determined to have impaired decision making capacity, the next issue is to identify whether there is a legally authorized representative. Documentation purporting to establish appointment as a legally authorized representative must be carefully evaluated to determine the validity of the appointment and scope of authority granted to make decisions regarding procedures involved in the research. If a subject has impaired decision-making capabilities and there is no advance directive, durable power of attorney for health care, or guardian then the ability of a next-of-kin to consent may be considered. The University's General Counsel's Office should be consulted if there are any questions. The appropriateness of the use of a next-of-kin needs to be assessed in relation to the risk-benefit analysis of the protocol. In assessing benefit, the importance of the knowledge never substitutes for the benefit to the subject.

## CHAPTER 19 – Other Vulnerable Populations

*This chapter includes information and safeguards for the inclusion of additional vulnerable populations in research*

The IRB recognizes that additional safeguards need to be included for other categories of participants who are likely to be vulnerable to coercion or undue influence such as students, persons who do not speak English, illiterate persons, and other classes of potential participants. The following information will assist investigators in addressing these issues within their context of the research.

### What Additional Protections Should Be Included for Non-English Speaking Participants?

**1. *It is important not to exclude non-English speakers from participating in research.***

An investigator who intends to include non-English speaking individuals must provide sufficient detail in the research protocol regarding the plan for inclusion, including the plan for obtaining informed consent and HIPAA Authorization (if applicable) and any other additional provisions during the study.

If an investigator intends to enroll participants who speak a language other than English, a translated version of the informed consent form and HIPAA authorization must be submitted to the IRB for approval prior to use. The Principal Investigator must provide the qualifications of the individual or the service that was used to translate the informed consent documents. The Principal Investigator may wish to delay translating the consent documents until the IRB has granted approval for the English version to avoid extra translation costs.

Participants who do not speak English must be given an informed consent document written in a language understandable to them. A person who is fluent in both English and the subject's language must participate in the informed consent process. If the person authorized to obtain informed consent in the research protocol is not fluent in the subject's language, an interpreter or interpreter service may be obtained.

It is not appropriate to have a subject's child or minor relative act as an interpreter, nor is it appropriate to have someone interpret or translate without knowing anything about the study. The interpreter should be an adult who understands the language/culture and research. Family members and friends of the potential subject may not act as the sole translation/interpretation source for enrollment and participation in a research protocol; as they are not familiar with technical jargon and/or research terminology, they may withhold information during the translation process or may change the meaning of what is said by the potential subject or research staff.

**2. *Research NOT actively recruiting participants who are Non-English speakers***

Many protocols include the provision to include individuals who do not speak English as they are often a part of the general subject population, though they are not the targeted population. As non-English speaking individuals are not the targeted population, often informed consent and HIPAA Authorization documents are not yet translated into other languages as the needed language is not yet known. A modification is required to be submitted and approved by the IRB prior to informed consent in native language.



Other study-related documents that will be filled out by the subject (e.g., log sheets, data collection forms, self-assessment tools, etc.) must also be translated into the subject's native language. If the study involves more than one study visit, a plan must be developed to ensure that an appropriate party is available to conduct all study visits in the subject's native language.

Prior to the release of any Protected Health Information (PHI) to non-CWRU personnel, the HIPAA Authorization must be translated and signed by the subject prior to the release of any information.

### **3. *Additional guidance regarding the informed consent process and documentation***

When informed consent is obtained from non-English speaking participants using a translated consent form all the following must be done:

- The translated consent document must be approved by the IRB and be provided to participants in language understandable to them.
- A translator who is fluent in both English and the language of the subject must be present if the person obtaining consent does not speak the language of the subject.
- The consent document must be signed and dated by the subject or the subject's legally authorized representative (unless the IRB has waived written consent).
- The consent document must be signed and dated by the person obtaining consent and, if the person obtaining consent does not speak the subject's language, by the translator.
- The process must be documented via the Sparta IRB application describing how the process will occur and who will be involved.

## **What Additional Protections Are Required When Recruiting University Students, Employees and/or Other Existing Relationships with Potential Research Participants?**

### **1. *Students and Employees***

The IRB considers university students and employees as vulnerable populations due to the power differential of an investigator being a faculty member and/or a staff of higher rank. Justification of the intention to enroll Case Western Reserve University employees or students must be provided in the protocol. The actions to prevent coercion or undue influence must also be detailed in the protocol. Anyone with an employment or academic relationship to CWRU must be informed that their participation in a study, or refusal to do so, will in no way influence their grades, class standing, employment, or subsequent recommendations. Employees must never be made to feel that their job, promotion, salary, or status in any way depends on participation in research studies.

The involvement of students or employees in studies also requires a statement in the consent form acknowledging that refusal to participate will have no influence on grades, recommendations or job status.

The Principal Investigator or any Co-investigator may not be responsible for directly recruiting and/or obtaining informed consent from any person under their direct supervision. Direct recruitment of students and employees may be undertaken using IRB approved recruitment text via standard recruitment methods (e.g., IRB approved text in the Daily, recruitment flyers placed in staff/student mailboxes).

It is Best Practice that the investigators and study team members not be recruited or enrolled in the study. This helps to maintain the integrity of the data and outcomes are objectively measured and





provisions are there with respect to recruitment, consent, and affirmation of eligibility (e.g., by someone knowledgeable about but not part of the investigator's study).

Research protocols that do not directly recruit CWRU employees or students and whereby the investigators would not have any knowledge of the person's affiliation with CWRU (e.g., the subject is not requested to disclose this information during the course of the research) do not need to include provisions in the protocol or consent form to address enrollment of this population.

**2. *Investigator's Own Client and/or Patient Population***

Some research protocols may involve recruitment from one's own clinical pool of patients. To avoid any potential for undue influence that may result from the healthcare provider-patient relationship, the informed consent process should not be conducted solely by a healthcare provider who has a clinical relationship to the patient that will be enrolled. An additional person should be available to confirm eligibility (e.g., Co-investigator) and cosign the checklist. If possible, someone who does not have a clinical relationship to the potential subject should act as the "person obtaining informed consent."

**3. *Family Members of the Study Team***

An investigator or any other member of the study team may not recruit and enroll any direct familial relation. Provisions must be made in the IRB approved protocol to allow for study personnel with appropriate expertise to recruit and enroll another study team member's direct familial relation(s).

## What Are Other Classifications of Participants That Need Additional Protection?

**1. *Illiterate/Visually Impaired Participants***

The IRB allows for illiterate persons who understand English and individuals who are visually impaired to participate in research studies. In these situations, the consent document must be read to the subject and the process documented in the research file. For an illiterate subject, the consent document should be subsequently signed by the subject "making their mark," for instance by placing an "X," on the signature section of the consent document in order to document their understanding. Please note that some visually impaired participants can sign consent forms. Investigators are obligated to collect a signature if possible unless a waiver of written documentation has been granted by the IRB. The IRB also requires a witness to be present to confirm the consent process has taken place. Both the witness and the person obtaining informed consent must sign and date the consent document. As such, there must be an additional signature line and date for the witness on the consent document.

**2. *Participants Who Are Mentally Capable of Consenting But are Physically Unable to Sign the Consent Document***

The IRB allows participants that are mentally capable of consenting to research studies but are physically unable to sign the consent document to participate in research as long as a witness is present. The witness must verify that the informed consent process has taken place and sign and date the consent document. In addition, if participants are capable of doing so, they must place a mark or cross on the signature line of the consent document to confirm their voluntary participation in the research study. This process must be documented in the research file. If the reason that prevented signing the consent form resolves, the subject should be asked to sign and date the consent form. Protocols actively enrolling individual participants who are physically unable to sign the consent document should include a witness line on the consent document.



### **3. *Other Vulnerable Adult Populations***

The IRB recognizes that the ability of adult populations to give voluntary informed consent may be compromised by circumstances. Such circumstances can include economical disadvantages, educational disadvantages, and physical handicap. The IRB will review the potential risks and benefits of each proposed protocol on a case-by-case basis to assure rights and welfare are protected, coercion is minimized, and the study is conducted with the utmost regards for ethical standards.

## **What Is Community Based Participatory Research?**

Community based research is research that is conducted as an equal partnership between academic investigators and members of a community. In Community Based Participatory Research (CBPR) projects, the community participates fully in all aspects of the research process, including the design and implementation of research, analysis and the dissemination of results, when appropriate. The relationship between community agencies and coalitions from the results will allocate resources, create systems, and revise policies, programs and practices.

Community is often self-defined, but general categories of community include geographic community, community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate. The CWRU IRB administrators will assist the investigator in developing such arrangements.

The CWRU IRB is very knowledgeable about CBPR protocols, assist researchers with their studies and provide guidance to help engage the community and be receptive from informal or formal consultation or input.

Help resources:

[Community Innovation Network | Case Western Reserve University](#)

[National Initiative on Mixed-Income Communities | Case Western Reserve University](#)

[Partnership for Evaluation, Research and Implementation \(PERI\) | Begun Center for Violence Prevention Research and Education | Case Western Reserve University](#)

Prevention Research Center for Healthy Neighborhoods at Case Western Reserve University ([prchn.org](http://prchn.org))

[First Year Cleveland|Every Baby Deserves to Celebrate a First Birthday](#)

<https://case.edu/cancer/community/community-outreach>

As a research community, improving community knowledge and cultural awareness of research at CWRU is a priority for our surrounding communities. The Case Comprehensive Cancer Center has a Community Advisory Board who specialize in community outreach to reduce the high rates of cancer and cancer deaths among underserved communities.

The CWRU HRPP seeks to understand and address the challenges facing the communities. In the efforts of CWRU researchers, research is used to rebuild trust, facilitate access and increase understanding to improve the aspects of health across the communities.

## CHAPTER 20 – Recruitment

This chapter includes information on appropriate recruitment methods for various types of studies

The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) consider subject recruitment to be the first component in the informed consent process. Recruitment of participants must be equitable and include racial, ethnic, educational, age, socioeconomic, and gender diversity appropriate to the research study. All recruitment efforts must respect personal rights to privacy and confidentiality and be compliant with HIPAA regulations, when applicable.

Recruitment procedures must be designed so that informed consent, parent/guardian permission, and assent are given freely, and there is no coercion or undue influence. In order to evaluate this, the IRB must know who the study participants will be, what incentive(s) is being offered, and the conditions under which a payment is issued. Financial payment, academic credit, gifts, gift cards, or raffles should be reasonable for the time, expenses, discomfort, or inconvenience of participating. The IRB must review all of the research documents and activities that bear directly on the rights and welfare of the participants of the proposed research, including the methods and material that investigators propose to use to recruit study participants. Recruitment information should be accurate and consistent with the IRB protocol.

### How to Ensure There Is an Equitable Selection of Participants

Both the benefits and risks of research participation must be equitably distributed. This is in line with the Justice principle of the [Belmont Report](#). Exclusion of any specific group (e.g., women of child-bearing potential) must be justified in the protocol. If non-English speaking individuals are not to be included in the study, justification is required. When recruiting vulnerable or special populations for study participation (e.g., university employees, students, and children), additional protections from undue influence or coercion are needed.

### How to Contact Potential Participants

A study team member may approach prospective study participants about participation in an IRB-approved protocol by multiple means. The method of obtaining names and contact information, who will contact the potential participants, how permission will be obtained from the treating physician, and how data confidentiality will be protected must be presented in detail in the protocol. The IRB must have assurance that any information collected about prospective participants will be appropriately handled. If the potential participant is not interested or eligible for participation, their contact information is kept confidential until no longer needed.

Scripts read by the researchers or other individuals assisting in the recruitment of participants must be submitted to the IRB for review and approval to assure that they adequately protect the rights and welfare of prospective participants. Examples of when scripts are needed include phone screeners, interacting with potential participants, or any presentation that communicates research study information.

In some special circumstances, individuals who are not formally listed on the protocol may be performing specific recruitment activities (such as a receptionist handing out flyers), but solely in the role of service



provider. In these cases, they should only be providing advertisement materials and researcher contact information.

**1. *Phone Recruitment***

A recruitment/cover letter or e-mail giving brief information about the study and informing the potential participant that they will be receiving a call from the study staff is recommended. In an effort to uphold the ethical principle of respect for persons, **cold calling is not encouraged**. In some situations, it may be most appropriate for an individual to be introduced to the study by someone with whom they already have a relationship. If the person is interested in participating, they can contact the study staff for more information.

**2. *In Person Recruitment***

Permission from a study site (e.g., school, factory or business) should be obtained before researchers approach prospective study participants. The IRB will want copies of letters of cooperation or IRB approvals from each study site prior to approval. In person recruitment must be done in a manner that protects the privacy of individuals, commensurate with the level of sensitivity of the research topic.

**3. *Electronic Media Recruitment***

All email and internet recruitment materials directed at potential participants are considered advertisements and the same rules apply. This includes information posted on social media websites (e.g., Threads, Facebook, YouTube, etc.), community boards, recruitment registries (e.g., Research Match), chat rooms, or other websites. Investigators are asked to provide the IRB copies of letters or emails of cooperation from electronic study sites.

Web forms may ask visitors to answer questions regarding eligibility for a specific study. If identifiable private information is collected via the website, the IRB will review plans for protecting the confidentiality of that information and ensure that the website clearly explains how identifiable private information might be used.

**4. *Secondary Recruitment***

Secondary recruitment refers to using a study participant to identify friends, family members or others with the intent to contact them as potential research participants. This is also known as snowball sampling. While there can be important research reasons that secondary recruitment is needed, it must be approached in a manner that respects the privacy of the potential participants. The study participant may give the study team's contact information to a potential participant, rather than providing the name of the potential participant to the researcher. Failure to hear from primary or secondary participants does not imply consent to further contact.

## How to Create Advertisements

Advertising materials are part of the recruitment process and should be submitted as part of the initial IRB application. Investigators must obtain IRB approval for all television, radio, videotape or print advertisements, posters, flyers, handouts, e-mail solicitations, websites, and other recruitment methods and materials intended for the recruitment of prospective participants in a research protocol.



The IRB pays particular attention to risk and potential benefit information to ensure it is presented in a balanced and fair manner. The information presented should not mislead, for example, by promising benefits or implying a benefit beyond that potentially provided by the research.

**1. *What May Be Included in Advertisements***

Any advertisement to recruit participants should be limited to the information the prospective participant needs to determine eligibility and interest. When appropriately worded, the following items may be included in advertisements:

- Statement that the study is research.
- The condition and/or the purpose of the research in summary form.
- The criteria that will be used to determine eligibility for the study in summary form.
- A brief list of participation benefits, if any (e.g., a no-cost health examination).
- The time or other commitment required of participants.
- The location of the research and the person or office to contact for further information.
- Compensation may be mentioned.

**2. *What Not to Include in Advertisements* (per AAHRPP Standards)**

- A statement or implication of certainty of a favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
- Claims, either explicitly or implicitly, that the research procedures are safe or effective, or that the research procedures are known to be equivalent or superior to any other procedure, method, technique, etc.
- Promise of a free service or item when the intent is only to say participants will not be charged for taking part in the research and/or when the investigator cannot provide or arrange a free service or item.
- Emphasize the compensation, by such means as larger or bold type.
- Include any exculpatory language.

## What Are Restrictions for Payment for Recruitment?

The IRB discourages the use of bonus payments and finders' fees for recruitment or identification of potential study participants. If payments for recruitment are proposed, the payment arrangements must not interfere with providing the prospective participants with sufficient opportunity to consider whether to participate. The protocol must explain what measures are taken to ensure that payments will not lead to undue influence or coercion of study participants. The IRB requires full disclosure of any financial arrangements that may encourage investigators to recruit participants for research participation that may not be in the subject's best interests.

Recruitment of study participants is an essential part of the research protocol and must be presented in sufficient detail to allow the IRB to fully assess the investigator's plan. Recruitment of participants must be equitable and include racial, ethnic, educational, socioeconomic, and gender diversity appropriate to the condition that is studied. Exclusion of any specific group (e.g., women of child-bearing potential) must be justified in the protocol. Both the benefits and risks of research participation must be equitably distributed.

All recruitment efforts must respect personal rights to privacy and confidentiality and be compliant with HIPAA regulations. The recruitment plan must avoid coercion of participants. Financial compensation, reimbursement for expenses, or other inducement for participation must not be coercive and should be

reasonable for the expenses, discomfort, or inconvenience of participating. In addition to IRB requirements, the HIPAA regulations put further restrictions on research recruitment activities.



## CHAPTER 21 – Ethics Consultations

### When Are Ethics Consultations Available or Required?

Research protocols that raise particularly complex ethical issues include vulnerable populations (e.g., decisionally impaired, mentally ill, and children participants, etc.) and/or are classified as greater than minimal risk with no prospect of direct benefit to the research subject. Examples of additional complex issues include but are not limited to international studies involving deviation from American standards of care, and studies involving greater than minimal risk with permanently or temporarily decisionally impaired participants.

The IRB provides consultation to investigators, at their request, concerning specific ethical issues or questions.

At the request of the IRB Chair or by a vote of the Board, a consultation may be requested as part of the review process of a protocol by the IRB. Additional outside ethics consultation may be requested prior to review of a protocol by the IRB. University departments may also refer their investigators to the IRB for review and recommendations.



## CHAPTER 22 – International Research

*This chapter includes information for when research is conducted internationally by U.S. investigators*

### When Is a Study Considered International Research?

The CWRU IRB has special provisions for investigators where some or all of the study participants are located outside of the United States. The CWRU IRB requires additional review for human subject research projects where some or all of the study participants are located outside of the United States.

All Human Research, regardless of funding, performed outside the United States must obtain appropriate institutional IRB approval according to federal regulations and the Federalwide Assurance (FWA). The University recognizes that the procedures normally followed in the foreign countries may differ from those set forth in this standard operating procedure. The research, however, may be approved if the procedures prescribed by the (foreign) institution afford protections that are at least equivalent to those provided in the FWA.

For international research, where CWRU IRB will serve as the IRB of record, the faculty and/or staff of CWRU must be ultimately responsible for the conduct of the research.

The CWRU IRB prefers that in international research appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, also review and approve the proposed research within the context of their own ethical requirements in addition to the CWRU IRB in order to help ensure that the research is culturally acceptable. The CWRU IRB usually requires documentation of approval from the host country/countries ethical review committee(s) prior to review and approval of the protocol.

Investigators must provide the same or equivalent protections to human participants in research they may conduct in countries outside the United States. When conducting transnational or international research, investigators must be aware of local laws and the cultural context in all locations where the research is conducted and comply with existing laws and adhere to cultural norms. OHRP provides a compilation of regulations and guidelines that govern human participants research in other countries, as well as standards from a number of international and regional organizations:

<https://www.hhs.gov/ohrp/international/compilation-human-research-standards/index.html>

### What Are Additional Requirements to Conduct International Research?

An International IRB protocol submission submitted for CWRU IRB review should identify whether there is a local IRB ethics Committee (EC), or government entity that will perform review in the host country.

- If local review has been conducted, a copy of the approval letter/notice should be included in the application.
- If local review has not been initiated or is still in process, this should be made clear in the application.



- Oversight by the local ethics board/IRB should include the following activities:
  - Initial review, continuing review, and review of modifications.
  - Post-approval monitoring.
  - Handling of complaints, non-compliance and unanticipated problems involving risk to participants or others.
- If the local IRB will not perform the required review functions, the CWRU IRB must fulfill the functions.

There are countries in which a local review board or government review mechanism is not available. In such cases, the CWRU IRB must obtain a consult from an individual who is familiar with the cultural background, local context, and community attitudes of the country in which the research will be conducted. This individual may not be associated with the conduct of the proposed research.

- It is the responsibility of the investigator to find consultants that have knowledge of the specific country and can provide a cultural review.
- The investigator should send the person's name and contact information to the CWRU IRB.

***Please note:*** The CWRU IRB will not take action to approve a protocol submission without either written documentation that local review and approval has been granted in the host country, or the consult requested by the IRB has been received and accepted.

The CWRU IRB may also utilize local experts knowledgeable about the social and cultural norms in its review of the protocol. For studies that are not greater than minimal risk, an expedited review of the protocol may be granted.

The convened IRB or designated reviewer may review and/or consult with University, local or national experts to determine if the research is appropriate based on the laws and knowledge of the country or community in which the research will take place and may consult the OHRP website publication, [\*The International Compilation of Human Research Protections\*](#), for in-country research information. All relevant CWRU IRB guidance applies to international research. In addition, international protocols should include the following information:

- Explanations of cultural differences that have influenced the study design or consent process.
- Rationale for conducting the study with an international population.
- Information regarding the host country's IRB, Ethical Review Committee, or equivalent organization.
- Letter(s) of agreement or IRB approval from the local host institution(s) to cooperate in the proposed research.
- A copy of the consent form (if used) in English and the appropriate native language(s).
- Information regarding the literacy level of the expected participants and how this may affect the informed consent process.
- A description of the informed consent process including methods for minimizing the possibility of coercion or undue influence in seeking consent and safeguards to protect the rights and welfare of vulnerable participants.
- If remuneration is given to participants, provide a justification for the amount of money or goods and how this relates to the average annual income of people in the host country.

The CWRU IRB encourages investigators to make provisions for the study population to benefit from the research study.

### ***Federally Funded Studies***

A Federalwide Assurance (FWA) is necessary to document that the international institution/performance site will conduct the research in accordance with U.S. federal policy.

## What Are Special Considerations for Consent in International Research?

- For studies involving populations that have no written language: use an English consent form as a template for translation and include a statement about the process for informed consent. The consent form should be signed by the interpreter, the study Principal Investigator, and the subject, who will make a mark or thumb print as appropriate.
- For studies where obtaining a signature is not culturally appropriate: the Principal Investigator may request a waiver of signature and provide justification for the waiver.
- For studies involving populations that utilize group consent: describe and justify the use of group consent. Provide a method to obtain private or individual subject assent. Provide a method of protecting those who choose not to participate in the study.
- Studies involving Children: the requirements for assent for Children in Research are applicable. The legal age for consent in other countries may differ from Ohio. The local legal age should be used for choosing consent versus assent documents.
- Translated Consent Documents: all consent forms and associated documents to be used with potential research participants must be translated into the appropriate local language and submitted to the CWRU IRB. The investigator must provide the name and brief description of the qualifications of the individual or the service that was used to translate the informed consent documents.

In general, the CWRU IRB does not require independent back translation of consent documents because the local context reviewers are usually able to read the local language and can review the content of the foreign language consent form. If the international site's ethical review committee (ERC) or IRB approves the translated documents, the CWRU IRB may accept these approved translations. For specific protocols the CWRU IRB may require back translation of foreign language consent forms.

The CWRU IRB prefers to have the translated consent form available at the time of IRB review. However, at the investigator's request, the CWRU IRB may allow waiting to have the translation done until after the approval of the English version. If this is done, the CWRU IRB will not approve the translated consent form until the accuracy of the translation has been reviewed.

## Does HIPAA Authorization/Privacy Rule Apply for International Research?

If the investigator or research study staff is responsible for, or involved with, the use and disclosure of protected health information (PHI) as defined by the HIPAA rule, then the federal regulations apply. It is the responsibility of the investigator to comply with HIPAA Authorization/Privacy Rule requirements if any protected health information that is transmitted back to the United States.



The HIPAA rule does not apply at research sites outside of the United States where individually identifiable information may be collected. Once the individual identifiable information is transferred to a HIPAA covered facility, this is rendered individually identifiable health information (PHI) by virtue of its being held by a facility covered by HIPAA. Once data is transferred to a HIPAA covered component, all HIPAA regulations apply.

## How Are Conflicts of Interest Considered for International Research?

No IRB member may participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. The IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

## CHAPTER 23 – Resources and Facilities

*This chapter contains information about research resources and facilities available for individuals conducting studies at CWRU*

### Clinical & Translational Science Collaborative (CTSC) FDA & Regulatory Support Core Under the UH FDA & Monitoring Support Core

The FDA & Regulatory Support Core are a team of dedicated support staff who are well versed in the regulatory approval and startup processes of the FDA and the Institutional Review Board (IRB). As a fee for service team, the FDA & Regulatory Support Core can provide flexible services based on the individual needs of each department/investigator and can begin at any point in the research trial.

Upon request, services from the core can begin immediately and be maintained on a short- or long-term basis. In addition, the FDA & Regulatory Support Core are available to provide consultation services prior to the start of a clinical trial to assist investigators with drug/device/biologic pre-clinical questions, biostatistical support, and guidance on the correct regulatory pathway with the FDA and IRB.

#### ***FDA support services include:***

- Protocol review and evaluation
- Drug and device risk determination
- IND/IDE application assistance
- Regulatory document/binder creation
- Source document creation
- FDA regulatory monitoring
- Long term FDA maintenance
- Biostatistical services

#### ***IRB application and study start-up support:***

- Regulatory document/binder creation
- Investigator and study team education/training
- Regulatory prep/clean-up for monitoring visits  
Long-term regulatory maintenance
- Study closure support

Any request for service can be sent to [FDAregsupport@uhhospitals.com](mailto:FDAregsupport@uhhospitals.com) or contact Heather Tribout, Manager, Research Support Core at [Heather.Tribout@UHhospitals.org](mailto:Heather.Tribout@UHhospitals.org).

#### ***Additional website links to the specific services:***

- More Information: <https://www.uhhospitals.org/uh-research/for-researchers/research-and-clinical-trials/core-offices/research-support/fda-and-monitoring-support>
- Services Request Form: [uhhospitals.org/researchsupportcore](https://uhhospitals.org/researchsupportcore)
- UH Mobile Research Unit: [uhhospitals.org/mobilecrc](https://uhhospitals.org/mobilecrc)



## CHAPTER 24 – Non-Compliance Involving Human Research

*This chapter describes the process that CWRU IRB follows to manage allegations and findings of non-compliance with human subject protection regulations*

### Definitions Pertinent to Non-Compliance

***Allegation of Non-Compliance:*** An unproven assertion of non-compliance; suspected non-compliance with human subject protection regulations, CWRU policies, or IRB requirements and determinations.

***Continuing Non-Compliance:*** A pattern of non-compliance that, in the judgment of the CWRU IRB Chair or convened IRB, indicates a lack of understanding of the regulations or institutional requirements that may affect the rights and welfare of subjects, would have been foreseen as compromising the scientific integrity of a study such that important conclusions could no longer be reached, suggests a likelihood that non-compliance will continue without intervention, or frequent instances of minor non-compliance. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance with human subject protection regulations.

***Non-Compliance:*** Any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with federal regulations or the requirements or determinations of the CWRU IRB. Non-compliance actions may range from minor to serious, be unintentional or willful, and may occur once or more than once. The degree of non-compliance is evaluated on a case-by-case basis and will take into account such considerations as to what degree subjects were harmed or placed at an increased risk and willfulness of the noncompliance. Examples include, but are not limited to:

- Failure to obtain CWRU IRB approval prior to recruitment and involvement of human subjects.
- Failure to obtain CWRU IRB approval for new study team members or protocol changes.
- Inadequate or non-existent procedures for the informed consent process.
- Inadequate supervision.
- Failure to follow recommendations made by the CWRU IRB.
- Failure to report adverse events or protocol deviations.
- Failure to provide ongoing progress reports.

***Serious Non-Compliance:*** An action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risks to subjects, decreases potential benefits, or compromises the integrity or validity of the research. Examples of serious non-compliance include, but are not limited to:

- Conducting non-exempt research without CWRU IRB approval.
- Enrollment of subjects that fail to meet the inclusion or exclusion criteria of the protocol.
- Enrollment of subjects that increase the risk to the subject.
- Enrollment of subjects while study approval has lapsed.
- Major protocol deviations that may place subjects at risk from the research.

***Minor Non-Compliance:*** Non-compliance that is neither serious nor continuing. An example of minor non-compliance includes failure to comply with IRB policies that are administrative in nature (for example, turning in a report of an unanticipated problem late, or failure to date a consent form).

## What Are The IRB Oversight Responsibilities to Evaluate Allegations of Non-Compliance?

The IRB, as part of their oversight responsibilities, must evaluate all non-compliance with human subject protection regulations and institutional policies and promptly report any serious or continuing non-compliance to the study sponsor and/or the HHS Office for Human Research Protections (OHRP). The IRB requires investigators to report all matters of potential non-compliance. If an allegation of non-compliance is reported from any source (including monitoring/auditing reports, subject complaints, internal allegation or investigator self-reporting), the CWRU Office of Research Administration, in consultation with the CWRU IRB and the University Compliance Officer, will make an initial assessment to determine:

- Whether there is sufficient information present to verify and determine if the allegation is true;
- Whether additional information is needed to make a determination; and
- Whether a determination of non-compliance is serious or continuing.

All reports of alleged non-compliance are investigated by the CWRU Office of Research Administration. If it is determined that the non-compliance might be serious or continuing, the suspected non-compliance is forwarded to a convened meeting for Full Board IRB review and determination.

Goals of investigating and managing issues of potential noncompliance include:

- Assuring the safety, rights, and welfare of human research subjects;
- Developing action plans to prevent recurrence and promote a culture for future compliance;
- Educating research staff to assure the understanding of HHS regulations and guidelines and IRB guidance; and
- Reporting serious or continuing non-compliance to the appropriate regulatory agencies and institutional officials.

### ***Identification and Investigation of Non-Compliance***

An allegation of non-compliance will result in the Research Compliance Officer conducting an investigation of the suspected non-compliance. Allegations and/or findings of non-compliance are identified in a variety of ways including notification by investigators, research team members, regulatory bodies, sponsors, research subjects, institutional personnel or committees, the public, or anonymous sources. The initial allegation may be presented orally. Findings of non-compliance may also be identified during routine Quality Improvement Program reviews.

### ***Unsolicited or Voluntary Notifications of Allegations or Findings of Non-Compliance***

When findings and allegations of non-compliance are reported to the IRB, it is initially reviewed by the Research Compliance Officer. The Office will review documentation and request additional information as needed. The Office of Sponsored Projects will be notified of the investigation if that office is responsible for managing any related federal funding to the protocol in question. If a detailed explanation does not accompany the report, the Research Compliance Officer or Manager of Regulatory Compliance Monitoring will contact the investigator to request additional information. The investigation will begin within 5 working days of learning of the recognized concern. The purpose of the investigation is fact-finding and may involve examination of study records and discussion with investigators, the research team, other personnel, research subjects, and others as appropriate. A communication will be sent to the investigator describing the issue or allegations, any interim immediate action, and a request for additional information.



If requested by the individual reporting the allegation, the IRB will attempt to keep their identity confidential. However, confidentiality cannot be assured. If an anonymous allegation is made, the IRB will decide if sufficient detail is available to determine if non-compliance occurred and whether the allegation can be investigated in the absence of an identified complainant.

***Allegations or Findings Identified by the CWRU IRB***

Allegation or findings of non-compliance identified during monitoring visits conducted by the Research Compliance Officer are reviewed with the IRB. The Research Compliance Officer and/or Manager of Regulatory Compliance Monitoring will prepare a written summary of the observations and a proposed action plan for the investigator. The IRB will review the summary at the next full review meeting.

The action plan may include any, or all of the following:

- SpartaIRB Reportable New Information submission regarding an Unanticipated Problem, Adverse Event, and/or Protocol Deviation Form for further review;
- Identifying the finding as minor non-compliance and request the Principal Investigator create a thorough [Corrective and Preventive Action Plan \(CAPA\)](#) to correct and/or prevent the event from occurring again;
- Require Human Subject Protection education;
- Require additional monitoring for the study in question and/or other studies conducted by the investigator;
- Temporary suspension or permanent closure/termination of the study.

Once the IRB is in agreement with the proposed action plan, the Principal Investigator will receive a determination letter that includes all monitoring observations, proposed action items, recommendations, educational requirements, and additional monitoring requests.

***Minor Non-Compliance***

The CWRU IRB staff will try to resolve reports of minor non-compliance with the Principal Investigator and research team. If the IRB staff cannot work out a corrective action plan with the investigator, then the report will be referred to the IRB for review and recommendations.

Allegations of minor non-compliance will be investigated by contacting the investigator and research team for verification. The IRB Office receives allegations or reports of non-compliance and will conduct the initial fact-finding and compile information. If non-compliance is clearly minor and the proposed action plan seems adequate, the IRB Office may handle the allegation or report by documenting the event and the proposed corrective action and reporting the incident to the CWRU IRB with no further action required. If, in the course of handling the allegation or report of non-compliance, the IRB Office becomes concerned that the non-compliance may be serious or continuing, the matter will be referred to the Associate Vice President for Research, IRB Chair, and IRB Vice Chair(s) for further action.

Upon completion of the initial fact gathering process, the IRB will issue one of the following determinations:

**Not Non-Compliance**

When the Chair/designee determines that the facts do not support a finding of non-compliance as defined in this guidance, the report of non-compliance will be dismissed, and no further action will be taken. The affected investigator(s) will be notified in writing of the determination.



### **Minor Non-Compliance**

When the IRB determines that the facts support a finding of minor non-compliance, the IRB will either approve the research to continue with no further action required or require study modifications.

The affected investigator will be notified in writing of the determination and the facts supporting the determination. No further action will be taken unless the Principal Investigator refuses to cooperate with the corrective action. Any required changes or modifications submitted by the investigator in response to the determination shall be reviewed by the CWRU IRB according to applicable policies on review of proposed changes in approved research. It is generally expected that these changes will be eligible for review according to the procedures on review of minor changes in approved research using the expedited review process.

### **Serious or Continuing Non-Compliance**

When the information regarding an alleged report of non-compliance indicates serious non-compliance, the information is forwarded to the full CWRU IRB for review, consideration of suspension criteria, or consideration of termination. An investigation by the IRB Office and the Research Compliance Officer can occur simultaneously with IRB review for consideration of suspension.

## **How Does The CWRU IRB Review Non-Compliance Reports?**

To assist in making a determination, a report outlining the facts surrounding the allegation and appropriate supporting documentation will be forwarded to all members of the CWRU IRB for review prior to a full board meeting. The following documents will be forwarded/accessible to all CWRU IRB members:

- A statement of the non-compliance allegation;
- Supporting documents including a copy of the current IRB approval letter, protocol and consent form(s) as applicable to the investigation;
- A statement of previous IRB administrative actions related to the non-compliance;
- Any relevant additional information or special circumstances;
- Assessment of increased risk (if any) to subjects resulting from the non-compliance;
- Recommendations for possible actions or resolution;
- Review of the status of the investigator's other IRB-approved protocols;
- The Grant or Funding Agreement, if applicable; and
- Any other pertinent information (e.g., questionnaires, DSMB/audit reports, etc.).

Any voting member of the IRB may serve as primary and secondary reviewers. The Research Compliance Officer and/or Manager of Regulatory Compliance Monitoring will present the materials at the convened IRB meeting. The IRB will then:

1. Review the information;
2. Vote on whether non-compliance has occurred based on the information provided, or defer the vote and gather additional information if needed from the investigator or others involved;
3. Vote on whether the non-compliance is serious; and
4. Vote on whether the non-compliance is continuing.

The discussion, determination, and vote will be recorded in the IRB meeting minutes. The minutes must also include a description of the non-compliance issue and allegations and also document the vote as to



whether the study is to continue with or without change, is suspended, or is terminated and whether corrective action is required.

Unless otherwise approved by the IRB, no guests/visitors may be present during the portion of the IRB meeting when a non-compliance matter is discussed. If an IRB member has or declares a conflict of interest regarding a specific investigator or protocol scheduled for a compliance discussion, they will leave the meeting while the non-compliance issue is discussed and will not vote on the issue.

After voting, the IRB may require:

- No action, protocol continues as previously approved;
- Modification of the study protocol;
- Modification of study documents;
- Modification of the study team member list;
- Modification of the informed consent process;
- Re-consent of subjects;
- Providing information about the non-compliance to current study subjects;
- Additional information be provided to past subjects;
- Obtaining more information pending a final decision;
- Modification of the continuing review schedule;
- Additional training of the investigator and research team;
- Monitoring of the research;
- Monitoring of the consent process;
- Suspension of the research (see below);
- Termination of the research (see below);
- Destruction of data collected at the time the non-compliance event occurred;
- Withdrawing or limiting the privileges of the investigator to conduct human research;
- Referral to other organizational bodies, as appropriate; and/or
- Other actions deemed appropriate.

The Principal Investigator will receive written notification from the IRB regarding the non-compliance issue, including recommendations for corrective actions. The IRB will maintain a file via SpartaIRB, including documentation and correspondence, on each non-compliance issue brought to the IRB for review. A report outlining any IRB determination of serious or continuing non-compliance will be submitted to the appropriate regulatory agencies and copied to the CWRU Institutional Official.

The IRB Chair or Vice Chair(s), using the expedited review process, may review and approve all minor modifications to previously approved research received in response to non-compliance. All modifications that are determined to be more than minor will be reviewed at a convened IRB meeting.

### **Suspension or Termination**

If the allegation concerns non-compliance that might be serious or continuing, the IRB may suspend research activities immediately until such time that the full IRB can convene if they believe that research subjects may be exposed to immediate harm. If in the opinion of the HRPP Organizational Official or the Institutional Official, the allegation concerns non-compliance that might be serious or continuing and research subjects may be exposed to immediate harm, they may immediately suspend institutional permission to conduct the research activities until such time that the full IRB



can convene. Suspension or termination of IRB approval of research will be reported to the appropriate regulatory agencies and institutional officials.

**Non-Compliance with HIPAA (Privacy Language Requirement)**

Failure to comply with HIPAA (Privacy Rule) requirements for research studies will be co-investigated by the Research Compliance Officer and the CWRU Director of Privacy Management.

Instances of non-compliance with HIPAA requirements that also constitute non-compliance with human subject research regulations will be reviewed by the IRB under non-compliance procedures.



## CHAPTER 25 – Quality Improvement Program (QIP) Reviews

### Overview of the Quality Improvement Program

CWRU Quality Improvement Program, managed by the Human Research Protection Program Office in the Office of Research Administration, aims to promote and ensure compliance with Human Research regulations and CWRU policy. The HRPP Office is responsible for implementing the Quality Improvement Program (QIP), which focuses on decreasing the risks to the University, protecting the safety and welfare of research participants, promoting standards of excellence in the conduct of research, identifying and communicating best practices, and ensuring compliance with requirements and ethical standards.

The Quality Improvement Program evaluates investigator and Institutional Review Board (IRB) compliance with applicable institutional policies and procedures, state laws and federal regulations for Human Research activities conducted or overseen by Case Western Reserve University. This process is also required by the University's Federalwide Assurance (FWA) with the Office for Human Research Protections (OHRP) and is a critical component of accreditation with Association for the Accreditation of Human Research Protection Program (AAHRPP).

The QIP includes the following functions:

- Evaluating Compliance of Active IRB Protocols
- Evaluating IRB Performance
- Responding to Complaints, Concerns and Questions
- Evaluating and Monitoring the Effectiveness of the HRPP
- Assessing Compliance with HRPP Policies and Procedures
- Identifying Areas and Implementing Measures for Improvement

### What Is a Quality Improvement Program (QIP) Review?

The QIP Review, also known as assurance auditing or study auditing, compares the implementation of the human research protocol by the Principal Investigator and their study team to the specifics of the CWRU Institutional Review Board (IRB) approved protocol. These reviews can be either routine (randomly selected) or for-cause (potential non-compliance). Any CWRU IRB-approved study determined to be engaged in Human Subject Research, regardless of IRB review type (i.e., Full Board, Expedited, or Exempt), may be selected for a QIP Review. Additionally, studies approved by UH or another IRB may be selected for a QIP Review if (a) the CWRU PI is the primary awardee (i.e., the grant is managed by CWRU) or (b) if an IRB of Record, sponsor, or regulatory agency requests an audit.

The process for the QIP Review begins with the HRPP Office sending the Principal Investigator and the Study Contact and/or PI Proxy (if applicable) an email message (written notification) that their study has been selected for a QIP Review and a request to schedule a meeting. Meetings may be in person or via Zoom, depending on the nature of the study (i.e., paper/hard copy documents vs. electronic documents). Investigators are asked to have a list of items available for review, which include but are not limited to the following:

- All executed informed consent documents, as applicable;
- A count of the total number of participants enrolled in the study to date;
- All data (e.g., files, subject records, questionnaires, surveys, etc.);



- Materials and/or documentation regarding subject feedback, including complaints, if applicable;
- Materials and/or documentation regarding participants who prematurely discontinued their participation or who were withdrawn by the PI, if applicable;
- Reports of all instances of adverse events and protocol deviations, if applicable;
- A list of all former and current study team members;
- A copy of the grant or funding agreement, if applicable; and
- The study Regulatory Binder.

Additional requests for information may be made during the meeting. The Principal Investigator and any relevant study staff (i.e., Project Manager or Study Coordinator) must be present to address questions and provide any requested documents for immediate resolution during the initial review.

The reviewer will discuss the research performed to date with the investigator(s) and study team, which includes relevant records, such as executed IRB approved informed consent documents and collected data. The reviewer also conducts a review of the IRB actions to ensure that they acted in accordance with all applicable federal, state and local requirements related to the protection of human participants. The QIP reviewer also checks for enrollment and consent dates to ensure commencement of research or study team member activities did not begin before all approvals required by the University were granted.

The QIP Reviewer will submit a report to the CWRU IRB that includes findings from both the investigator and IRB actions review. The IRB reviews the report and determines if any additional IRB actions are necessary. A copy of the report is also submitted to the HRPP Executive Director, who is responsible for addressing non-compliance by the IRB and reporting incidences to the Senior Vice President for Research, who is listed as the Institutional Official on CWRU's FWA. The Research Compliance Officer also receives a copy of the report so they can keep apprised of the findings. **All information obtained from the review is kept confidential and is shared only with necessary parties.**

The QIP Reviewer works with the Principal Investigator, Co-Investigator(s) and the study team to address and resolve any problems found during the review to get the study back into compliance with the outlined CWRU IRB approved protocol. Additionally, if the IRB asks for additional education or sanctions for the Responsible Investigator, Co-Investigator(s) and the study team members, the QIP Reviewer works with the Research Compliance Officer to establish these measures and helps to facilitate their completion.

## CHAPTER 26 – Overview of ClinicalTrials.gov Records

### What Is ClinicalTrials.gov?

ClinicalTrials.gov is a web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH).

### What Is a Clinical Trial?

A clinical trial is a research study in which one or more human participants are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

NIH provides these four questions to help determine the difference between a clinical study and a clinical trial:

1. Does the study involve human participants?
2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?

Please note that if the answers to the 4 questions are yes, the study meets the definition of a clinical trial, even if...

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention
- Only one aim or sub-aim of your study meets the clinical trial definition

Please note these types of studies are not considered a clinical trial:

- Studies intended solely to refine measures
- Studies that involve secondary research with biological specimens or health information

Any study that meets the definition of a Clinical Trial, is supported by a [Common Rule agency](#), or intends to publish in a journal overseen by or affiliated with the [International Committee of Medical Journal Editors](#), is required to be registered on ClinicalTrials.gov in accordance with the policies governing that site.

### What Are the FDA Requirements for ClinicalTrials.gov?

The Food and Drug Administration Amendments Act of 2007 (FDAA) requires registration and results reporting of all Applicable Clinical Trials (ACTs). An ACT is defined as:

- Interventional studies;
- Studies that require an IND or IDE;



- Studies where AT LEAST ONE or more of the following applies;
  - At least one site in the US or one of its territories, or
  - Study is conducted under an IND or IDE, or
  - The product is manufactured in and exported from the US or one of its territories.
- Studies that evaluate at least one drug, biological, or device product regulated by the FDA
- Studies that are not Phase 1 (drug and biological products\*) or not Device Feasibility (device products\*\*)

\*Phase 1 studies of new drugs are usually the first that involve people. Phase 1 studies are done to find the highest dose of the new treatment that can be given safely without causing severe side effects

\*\*Device Feasibility are usually 10 or fewer people to test the safety/efficacy of the device and has to meet very specific criteria to fit feasibility.

Email: [cwru-irb@case.edu](mailto:cwru-irb@case.edu) for more information.

The Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial can be found at the following website:  
[https://prsinfo.clinicaltrials.gov/ACT\\_Checklist.pdf](https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf)

## What Are NIH and Federal Funding Requirements for ClinicalTrials.gov?

The National Institutes of Health (NIH) Policy on Dissemination of NIH-Funded Clinical Trial Information requires registration and results reporting, and applies to all clinical trials funded by NIH, regardless of whether they are subject to the FDAAA 801 and the Final Rule effective January 18, 2017. The Policy is effective for competing applications and contract proposals submitted on or after January 18, 2017, and states that all NIH-funded awardees and investigators conducting clinical trials will register and report the results of their clinical trials on ClinicalTrials.gov. Please refer to the following grants policy information from NIH's Office of Extramural Research to learn more about ensuring compliance with NIH's implementation of FDAAA 801: [Requirements for Registering & Reporting NIH-Funded Clinical Trials | Grants & Funding](#)

Other Common Rule Signatories may require ClinicalTrials.gov registration and reporting. These include frequent CWRU collaborators, such as Department of Defense, Department of Education, and National Science Foundation. A list of signatories can be found here: [Federal Policy for the Protection of Human Subjects \('Common Rule' | HHS.gov\)](#) CWRU encourages all clinical trials, regardless of funding, register their studies. However, it is recommended that Principal Investigators check directly with their funding agency for their specific ClinicalTrials.gov requirements.

## What Is The International Committee of Medical Journal Editors (ICMJE) and What Are Their ClinicalTrials.gov Requirements?

The International Committee of Medical Journal Editors (ICMJE) is “a small working group of general medical journal editors whose participants meet annually and fund their own work on the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.” See <https://www.icmje.org/about-icmje/>



The ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trial's registry before the time of first patient enrollment as a condition of consideration for publication. While the ICMJE official members are currently limited to the list below, **any journal may state that they follow the ICMJE recommendations and, therefore, deny publication for studies not registered on ClinicalTrials.gov.** See <https://www.icmje.org/journals-following-the-icmje-recommendations/> for a list of publications that follow ICMJE recommendations. ***Please note:*** the absence of a journal/publication in this list does NOT guarantee that they don't follow ICMJE recommendations. CWRU encourages ClinicalTrials.gov registration of all clinical trials, regardless of intended publisher. It is also recommended that investigators check with their intended publisher(s) to determine journal requirements.

Current ICMJE Member List as of 11/1/2024 (see <https://www.icmje.org/about-icmje/>)

- Annals of Internal Medicine
- British Medical Journal
- Bulletin of the World Health Organization
- Deutsches Ärzteblatt (German Medical Journal)
- Ethiopian Journal of Health Sciences
- JAMA (Journal of the American Medical Association)
- Journal of Korean Medical Science
- المجلة الطبية التونسية (Medical Tunisia)
- Medwave
- Nature Medicine
- New England Journal of Medicine
- New Zealand Medical Journal
- PLOS Medicine
- The Lancet
- U.S. National Library of Medicine
- World Association of Medical Editors

## Which Office Can Help With ClinicalTrials.gov Records?

Please contact the CWRU HRPP Office's Quality Improvement Program ([irbqip@case.edu](mailto:irbqip@case.edu)) for help with ClinicalTrials.gov record processes:

- Requesting a new CWRU ClinicalTrials.gov account
- Resetting a user account password
- Registering a new record
- Completing a modification to/editing the record
- Composing annual updates
- Reporting results
- Uploading informed consent forms and protocol documents

***Please note:*** University Hospitals maintains their own UH ClinicalTrials.gov account. Generally, the ClinicalTrials.gov administrative organization (i.e., which organizational account you will register your study under) will depend on where the funding is directed: CWRU or UH. However, please check with the CWRU and UH IRBs if you have any uncertainty regarding which organizational account under which to register.

## How to Register a New Study

Studies that meet the HHS definition of a clinical trial, the FDA definition of an ACT, receive funding from a Common Rule agency, and/or plan to publish with an ICMJE member or affiliate **must have their study registered on ClinicalTrials.gov prior to the first study participant enrollment**. Please make sure that you have a plan in place for registering your study as soon as possible.

For step by step instructions on how to register a study please see the ClinicalTrials.gov guided tutorials <https://clinicaltrials.gov/submit-studies/prs-help/prs-guided-tutorials#/>

Data element definitions for the record sections and components can be found here: [Protocol Registration Data Element Definitions for Interventional and Observational Studies | ClinicalTrials.gov](#)

## What Are the Requirements for CT.gov Record Maintenance?

Once a trial is registered, information must be updated at least once every 12 months or sooner, according to the requirements below:

- If changes affect human subjects via a protocol modification (i.e., eligibility criteria, change in outcome measures, alteration of study arms or interventions), the information must be updated within 30 days of the IRB's approval.
- The record must be updated within 30 days of any changes in recruitment status or completion of study.
- Primary Outcome results need to be submitted no later than 1 year after the trial's Primary Completion date.
- ALL RESULTS, including Adverse Events, must be submitted no later than 1 year after the Study Completion date.
- The record must be updated within 15 days of a change in approval or clearance status of drugs and devices not previously approved by FDA.
- ClinicalTrials.gov PRS Review Comments and Record Errors will need to be addressed and/or corrected as applicable.

## What Are Results Reporting Requirements?

All Applicable Clinical Trials and federally funded clinical trials must have primary outcome results reported in their ClinicalTrials.gov records within one year of the primary completion date (PCD). The PCD is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome. Secondary outcome results and adverse events must be reported within one year after the Study Completion Date (SCD). The SCD is the date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events.

When the record's Overall Recruitment Status is changed to "Completed," "Terminated (Halted Prematurely)," or "Withdrawn (No Participants Enrolled)," copies of the most recent IRB-approved versions of the study protocol and consent form must be uploaded to the record within 60 days of the recruitment status change.





Please note:

- ALL data is required to be posted within 1 year of your Study Completion Date (SCD).
- If you are required to report results, **they must be entered by these dates, even if you have not yet published the data**. ClinicalTrials.gov will not grant extensions due to publication timing.
- The study protocol is REQUIRED to be submitted with results submissions on all Applicable Clinical Trials and federally funded clinical trials.
- You can also find out more information regarding results reporting in the ClinicalTrials.gov Protocol Registration and Results System (PRS) Guided Tutorials: [ClinicalTrials.gov PRS: Help: Results Data Entry](#)

## CHAPTER 27 – Reportable New Information

### Definitions Pertinent to Reportable New Information (RNI)

**Unanticipated Problem** is an event that could adversely affect the rights, safety or welfare of the participants, or others (e.g., family members, by-standers, and researcher/team) or which significantly impacts the integrity of research data.

An example would be a breach of confidentiality or unintentional destruction of study records.

**Adverse Event** is any unintended negative experience associated with the study materials or research procedures. Adverse events include both physical and psychological harms. Although they most commonly occur in the context of biomedical research, they also can occur in the context of social and behavioral research.

**Serious Adverse Events** are adverse events that result in any of the following outcomes: death; a life-threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect.

In addition, events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

**Non-Serious Adverse Event** is any event that causes interference with routine daily activities without major discomfort and these interferences do not persist.

Non-serious events also include events that that are easily tolerated and do not affect participation in routine daily activities.

**Protocol Deviation** is any alteration/modification to the IRB-approved protocol, whether intentional or inadvertent, that is not approved by the IRB prior to its initiation or implementation.

**Minor Protocol Deviation** is an incident involving noncompliance with the protocol but one that typically does not have a significant effect on the subject's rights, safety, welfare, or on the integrity of the resultant data.

**Major Protocol Deviation** is a more serious incident involving noncompliance with the protocol, usually involving critical study parameters. Major protocol deviations generally affect the subject's rights, safety, welfare, or the integrity of the study data.

**Protocol Exception** is a temporary deviation from the protocol that has been approved by the IRB before its initiation. Protocol exceptions are usually for a specific subject (e.g., allowing enrollment of a subject who is close to, but outside of, the age eligibility).

***Minimal Risk*** means that both the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102 (j)).

## What Are Reporting Requirements for Investigators?

Federal regulations 45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1) require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to participants or others. The IRB complies with all applicable local, state, and federal regulations in the conduct of human research studies.

In keeping with these regulations, investigators are required to promptly report any unanticipated problem, adverse event or protocol deviation, with special attention to deviations involving risks to participants or others.

- Researchers are responsible for knowing and following the IRB’s reporting requirements.
- When researchers rely on an external IRB other than the CWRU IRB, they are responsible for knowing and following the reporting requirements of the reviewing IRB.
- Information items that fall into one or more of the categories listed below must be reported to the IRB.
  - Investigators and study team members may submit Reportable New Information (RNI) to the IRB.
  - The author of the RNI will be listed as the point of contact for the RNI Submission.
  - All communications will occur between the IRB and that individual.
- These information items will be reviewed by the IRB to determine if they represent non-compliance, unanticipated problems involving risks to participants or others, and/or result in action items, suspension, or termination of IRB approval.
- Do not include any identifiable information related to participants in the submission or supporting materials.
- Maintain electronic copies of all information submitted to and received from the IRB.

For information on how to submit an RNI form in SpartaIRB, see [How To Submit Reportable New Information](#).

*When CWRU IRB is the IRB of Record for a Study:*

***What Should Be Reported Within Three (3) Business Days\* to the CWRU IRB?***

\*Within 3 business days of discovery

- Events that occur in studies involving drugs or biologics and are
  - Probably caused by or associated with study participation; and
  - Unexpected; and
  - Immediately life-threatening or severely debilitating to current participants or others not participating in the study
- Events that occur in studies involving testing of devices and are
  - Not previously identified in nature, severity, or frequency in IRB documentation (e.g., protocol, consent documents) OR relates to participants’ rights, welfare, or safety; and



- Immediately life-threatening or severely debilitating to current participants.

***What Should Be Reported in Five (5) Business Days\* to the CWRU IRB?***

\*Within 5 business days of discovery

- Information that indicates a new or increased risk, or a new safety issue. For example:
  - New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) that indicates an increase in the frequency or magnitude of a previously known risk or a new, previously unknown risk.
  - Revision to an investigator brochure, package insert, or device labeling that indicates an increase in the frequency or magnitude of a previously known risk or describes a new, previously unknown risk.
  - Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
  - Protocol deviation that harmed participants or others or that indicates participants or others might be at increased risk of harm.
  - Complaint that indicates participants or others might be at increased risk of harm or at risk of a new harm.
  - Any changes significantly affecting the conduct of the research.
  - Any adverse event which is both unexpected and related or possibly related to the research procedures, involves increased risk to the participant or others, and is considered an unanticipated problem.
    - An adverse event is “unexpected” when its specificity or severity are not accurately reflected in the IRB approved informed consent document or protocol, or are not expected given the characteristics of the subject population being studied
    - An adverse event is “related to the research procedures” if it was more likely than not to be caused by the research procedures, or if it is more likely than not that the event affects the rights and welfare of current participants.
- Non-compliance with the federal regulations governing Human Research or with the requirements or determinations of the IRB, or an allegation of such non-compliance. For example:
  - Implementation of study procedures, forms, or study team members prior to IRB approval.
  - Enrollment of participants who do not meet the study eligibility requirements.
  - Failure to obtain informed consent prior to initiation of study procedures.
  - Enrolling more participants than indicated in the IRB approved protocol.
- Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g. FDA Form 483).
- Written reports of study monitors, if applicable.
- Major failure to follow the protocol (major protocol deviation) due to the action or inaction of the investigator or research staff.
- Incarceration of a participant in a study not approved by the CWRU IRB to involve prisoners.
- Breach of confidentiality.



*When CWRU IRB is NOT the IRB of Record for a Study:*

***What Should Be Reported in Five (5) Business Days to the CWRU IRB?***

- All external events reported to a CWRU PI must be promptly reviewed by the PI and any event that changes the risk/benefit ratio of the study must be reported as information that indicates a new or increased risk.
- If protocol or consent form changes must be made due to a revised risk profile those changes should be submitted to the IRB as soon as possible.

External events where the CWRU investigator is not responsible for the reporting of the event to a regulatory agency are expected to have review as described in the Data and Safety Monitoring Plan (DSMP) for the protocol.

**Please Note:**

- All internal, unexpected, study-related deaths must be reported to the IRB within five business days of their discovery.
- Both internal, expected, study-related or non-study-related deaths and internal, unexpected, but not study-related deaths should be retained in the Principal Investigator files.
- Failure to report in a timely manner may be considered a compliance matter and referred to the IRB for review and a compliance determination.

**Any event that does not fit into the above categories does not need to be reported on an RNI form but is required to be reported in the study's yearly Continuing Review or Annual Check-in, regardless of IRB of Record. Study sponsors may have different reporting requirements than the IRB and it is the PI's responsibility to be knowledgeable about, and meet, the study reporting requirements.**

All RNI submissions are initially reviewed by the IRB and sent for Convened Board review as required. Board determinations will be reported to outside agencies as required. RNIs may require a QIP Review, the findings of which will be presented to the Convened Board. For more information see *CHAPTER 24 – Non-Compliance Involving Human Research* and *CHAPTER 25 – Quality Improvement Program (QIP) Reviews*.

**Administrative Hold**

The Principal Investigator may initiate an Administrative Hold while the RNI is being evaluated and related study modifications are being reviewed for approval. An Administrative Hold is a voluntary action by an investigator to temporarily or permanently suspend some or all research activities, such as recruitment, informed consent, or specific study procedures.

Although the investigator may discuss this action beforehand with the IRB Chair, Executive Director for the Human Research Protection Program, or the Senior Vice President for Research, the hold must be initiated voluntarily by the investigator and must not be used to avoid IRB mandated suspension or termination of reporting requirements.

- During administrative hold, the research remains subject to continuing review and requirements for reporting non-compliance and unanticipated problems involving risks to participants or others.
- Administrative holds must not be used to avoid reporting deficiencies or circumstances that otherwise require reporting by federal agencies.

- Administrative holds are not considered suspensions or terminations, and do not meet reporting requirements to OHRP, FDA, and other federal agencies.

## Protocol Deviations

Protocols must be conducted under the terms and specifications of the study as approved by the IRB.

- An investigator may not deviate from the requirements for procedures or testing of participants as outlined in the protocol.
- Protocol Deviations must be reported by the PI to the IRB in a timely manner.
- Major Deviations (see definition and examples below) are reported to the IRB within five business days of discovery.
- Minor Deviations (see definition and examples below) are kept in the investigator's file to be reported at the time of Continuing Review or Annual Check-in.

Deviations are reported in SpartaIRB using the appropriate category on the RNI form (see [How To Submit Reportable New Information](#)).

- Frequently, the most appropriate category is “Non-compliance” or “Researcher error,” but this is not all-inclusive and other categories may be more applicable depending on the nature of the situation.
- The author of the RNI should briefly explain the deviation and the corrective actions taken to avoid future deviations.
- If a change in the protocol, consent form, or the risk/benefit ratio for the study is needed, questions 5b. and 5c. should be answered appropriately and
  - A modification to the protocol will be required to be submitted via SpartaIRB.
  - The modified protocol, consent form, along with other revised study documents should be uploaded in the modification submission.

All protocol deviations are initially reviewed by the IRB Office. Deviations that result in harm to the participant are presented and reviewed at a Convened Board meeting.

Failure to report a major protocol deviation in a timely manner will result in a possible non-compliance review by the CWRU HRPP Office and forwarded to the CWRU IRB for determination and action item requirements.

**Major Protocol Deviation** is a serious incident involving noncompliance with the protocol usually involving critical study parameters. Major protocol deviations generally affect the subject's rights, safety, or welfare, or the integrity of the study data. Use the [Protocol Deviation Log template](#) to help determine if a protocol deviation meets the Major Deviation standard and 5-day reporting requirement.

### *Examples of Major Deviations*

- Failure to obtain informed consent, i.e., there is no documentation of informed consent or informed consent was obtained after initiation of study procedures;
- Informed consent obtained by someone not approved to obtain consent for the protocol;
- Use of invalid consent form, i.e. consent form without IRB approval, or outdated version that is missing current IRB approved information;
- Enrollment of a participant who was ineligible for the study;
- Performing a research procedure not in the approved protocol;
- Failure to report serious adverse event to IRB; sponsor; and/or regulatory agencies;





- Study medication dispensing or dosing error;
- Failure to follow the approved study protocol that affects participant safety or data integrity (e.g., study visit missed or conducted outside of required timeframe, or failure to perform a laboratory test);
- Failure to follow safety monitoring plan;
- Continuing research activities after IRB approval has expired;
- Use of recruitment procedures that have not been approved by the IRB;
- Participant giving study drug or device to a third-party;
- Enrolling significantly more participants than proposed in the IRB protocol (defined as over-enrollment by 10% or more);
- Any deviation that impacts the risk / benefit ratio

**Minor Protocol Deviation** is an incident involving noncompliance with the protocol but one that typically does not have a significant effect on the subject's rights, safety, welfare, or on the integrity of the resultant data. Minor deviations should be reported during the study's next Continuing Review or Annual Check-in.

**Examples of Minor Deviations**

- Missing original signed and dated consent form (only a photocopy available);
- Missing pages of executed consent form;
- Failure to follow the approved study protocol that does **not** affect participant safety (e.g., study procedure conducted out of sequence, failure to perform a required test, missing laboratory results, study visit conducted outside of required timeframe);
- Use of consent forms that are outdated/expired but contain the same information as the current consent;
- Failure of a participant to return study medication or device.

## Unanticipated Problems

Unanticipated Problems are events that could adversely affect the rights, safety, or welfare of the participants or others (e.g., family members, by-standers, and researcher/team), or which significantly impacts the integrity of research data. An example would be a breach of confidentiality or unintentional destruction of study records.

Specifically, an Unanticipated Problem is any incident, experience, or outcome that meets all 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; and
- **Related or possibly related to participation in the research** (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- **Suggests that the research places participants or others** (which may include research staff, family members, or other individuals not directly participating in the research) at a greater risk of harm



(including physical, psychological, economic, or social harm) related to the research than was previously known or expected.

Unanticipated Problems may or may not be classified as Adverse Events. For additional information, see OHRP's guidance here: [Unanticipated Problems Involving Risks & Adverse Events Guidance \(2007\) | HHS.gov](#)

There are types of incidents, experiences, and outcomes that occur that represent Unanticipated Problems, but are **not** considered Adverse Events or Protocol Deviations. For example, some Unanticipated Problems involve social or economic harm instead of the physical or psychological harm associated with Adverse Events. In other cases, Unanticipated Problems that are not Adverse Events may also place others at increased risk of harm, but no harm occurs to the participant themselves.

The primary responsibility for the evaluation of Unanticipated Problems lies with the investigator of the protocol. This includes the documentation, investigation, and follow-up of these events. The [Unanticipated Problem Log](#) can be used to fulfill the documentation requirement.

**For those events that require reports to the IRB it is the investigator's responsibility to submit the reports within five (5) business days of discovery of the problem or event. These are events that involve risk of harm or actual harm occurring to participants or others.** The investigator must complete the Reportable New Information (RNI) Form via SpartaIRB. Failure to report an Unanticipated Problem in a timely manner may be considered a compliance matter and referred to the IRB for review and a compliance determination. If the Unanticipated Problem does not meet the risk of harm or actual harm criteria, then the event does not meet the 5-day reporting criteria and should be retained in the investigator's file for reference as well as reported during the study's next Continuing Review or Annual Check-in.

The following are examples of Unanticipated Problems that need to be reported to the IRB within five (5) business days of the investigator learning of the event:

- Information that indicates a change to the risks or potential benefits of the research.
- A breach of confidentiality including inappropriate disclosure, lost, or stolen confidential information.
- Changes to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
- Incarceration of a subject in a protocol not approved to enroll prisoners.
- A participant becoming pregnant while enrolled in a study with pregnancy as an exclusion criterion.
- Disqualification or suspension of an investigator.
- Complaint of a subject when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- Protocol deviation (including accidental or intentional protocol deviation) that caused harm to participants or others or indicates participants or others are at increased risk of harm.

## Adverse Events

An adverse event is any unintended negative experience associated with the study materials or research procedures. Per OHRP, an Adverse Event includes any event meeting the following definition:

- 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.

- An adverse event encompasses both physical and psychological harms and, although they most commonly occur in the context of biomedical research, they can also occur in the context of social and behavioral research.

Adverse Events can be categorized as Expected or Unexpected. To make this determination, it is necessary to know the underlying condition of the subject including co-morbidities, and the severity and frequency of events in subjects who qualify for the study.

An **Expected Adverse Event** meets one or more of the following criteria:

- Attributed to the underlying condition of the subject being studied.
- Attributed to the subject population being studied.
- Identified in the literature, investigator brochure, other risk documentation, or informed consent.

An **Unexpected Adverse Event** meets one or more of the following criteria:

- Not listed in the informed consent, protocol, or other study documents.
- Not attributed to the underlying condition of the subject taking into account co-morbid conditions.
- Not attributed to the subject population.
- Severity and/or frequency of the event are beyond the range previously known.

For reporting requirements, see above, Page 174 and 175, *What Should Be Reported Within Three (3) Business Days\*/What Should Be Reported Within Five (5) Business Days\* to the CWRU IRB?* For all reporting periods "days" refers to business days after the investigator learned of the event. All reportable events need to be reported to the IRB within the timeline **even if the information about the event is incomplete**. Further information can be added with a follow-up report.

Failure to report an Adverse Event in a timely manner may constitute non-compliance and will be referred to the IRB for review as possible non-compliance, which will be processed as described in the CWRU IRB Non-Compliance document.

### **Serious Adverse Events**

A Serious Adverse Event (SAE) is specifically related to an OUTCOME and is one that has serious health implications and/or may jeopardize the health of the participant. Adverse Events that result in the following are considered SAEs:

- Death
- Life-threatening conditions or situations (i.e., the participant was at a substantial risk of dying)
- Hospitalization
  - Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes
- Disability or Permanent Damage (i.e., persistent or permanent change, impairment, damage, or disruption in the patient's body function/structure, physical activities, and/or quality of life.)
- Congenital Anomaly/Birth Defect



- Required Medical or Surgical Intervention to Prevent Permanent Impairment or Damage
  - Usually related to use of an investigational medical product (drug or device)
- Other Serious (Important Medical Events)
  - Would include events that do not fit the above categories but may potentially jeopardize participants' health, ability, or quality of life

Categorizing the severity of an Adverse Event is helpful in determining the seriousness of the event but should not be used to exclusively make that determination. Adverse Event severity is specifically related to the INTENSITY of the event:

- **Mild:** Easily tolerated symptoms of a minor irritant type causing no loss of time from normal activities. Does not require intervention.
- **Moderate:** A low level of inconvenience or concern; may interfere with daily activities, may require simple therapeutic intervention.
- **Severe:** Incapacitating; interrupts normal daily activities and generally requires systemic therapeutic intervention or hospitalization.

A Severe Adverse Event may or may not be a Serious Adverse Event. For example:

- After a participant is administered a study drug, they experience dyspnea and, after presenting to the emergency room, are admitted to the hospital for systemic treatment. This is both a Serious and Severe Adverse Event.
- After a participant is fitted with a wearable study device, they experience a painful, widespread rash which prevents them from carrying out their normal daily activities. They receive treatment and ongoing follow up from an outpatient healthcare provider. The rash resolves and the participant is left with non-permanent scarring. This is a *Severe* Adverse Event but, as the rash was not life threatening and did not result in permanent damage, it is NOT a Serious Adverse Event.

The primary responsibility for the evaluation of Adverse Events lies with the investigator of the protocol and must be done promptly. This includes the documentation, investigation, and follow-up of these events. The [Adverse Event Log](#) can be used to document events, categorize severity, and help determine expected vs unexpected events. For those events that require reports to the IRB, it is the investigator's responsibility to submit the reports in a timely manner. If new risks to the subjects are identified they must be included in a revised consent form.

Any Adverse Event that changes the risk/benefit ratio of the study or requires a change in the protocol or consent form, must be reported to the IRB within 3 business days. The investigator must make the protocol changes as soon as possible and submit the revised documents via a Modification in SpartaIRB.

Other events are reported as follows:

- All fatal events must be reported to the IRB as soon as the investigator learns of the event, if the investigator believes the event to be related or possibly related to the study. If the death is definitively determined to be unrelated to the study, it must be reported at the time of next Continuing Review or Annual Check-in.
  - Deaths which occur after the subject's research participation has ended do not need to be reported to the IRB unless the death is related to study participation.



- All Serious Adverse Events must be reported as soon as the investigator learns of the event.
- All Expected Adverse Events and summary reports are kept in the investigator's files and do not need to be reported to the IRB. The IRB does not require the investigator to report adverse events that occur to subjects enrolled in an observational study or non-interventional study unless the event is related to study participation, causes a change in study design, or increases risk for other subjects.
- If a subject has an Adverse Event after completing all of their study activities, and the study remains open at CWRU for other subjects, the adverse event is only reported if it was study related.
- If a CWRU investigator is notified about an event that occurred at another site in a study related to, but not the same as, the CWRU protocol, and the event results in a change in the protocol, consent form, or the risk/benefit ratio, the Adverse Event must be reported within 3 business days of learning of the event.
- If the change in the CWRU protocol is due to publication of results from another study which has an adverse impact on the CWRU protocol, it should be reported as soon as the investigator learns of the valid publication.
- The investigator who conducts research projects funded by a federal agency is obligated to report Adverse Events that are Serious and Unanticipated simultaneously to both the federal agency and to the IRB. The IRB has a separate and distinct obligation to report the adverse events to government authorities

### **Reporting of Adverse Events at Continuing Review or Annual Check-in**

Adverse events that do not result in a change in the protocol, consent form, or the risk/benefit ratio are reported to the IRB at the time of the next Continuing Review, Annual Check-in, or Study Closure. The Continuing Review form in SpartaIRB requests supporting documentation detailing any adverse events occurring since the last IRB review.

The Principal Investigator should provide an assessment of whether the Adverse Events present any additional risks to study subjects. Any additional risks to subjects must be included in a revised study protocol and informed consent forms submitted as a Modification in SpartaIRB.

## CHAPTER 28 – Reliant Review Agreements for Single IRB Review

### What Are the Bases for Single IRB Review?

The National Institutes of Health (NIH) and other Common Rule agencies expect that all sites participating in multi-site studies involving non-exempt Human Research funded by the NIH will use a single Institutional Review Board (sIRB) to conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects at 45 CFR Part 46.

- This policy applies to the domestic (USA) sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt Human Research, whether supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program.
  - It does not apply to career development, research training or fellowship awards.
- This policy applies to domestic awardees and participating domestic sites. Foreign sites participating in federally funded, multi-site studies will not be expected to follow this policy.
- Exceptions to the policy will be made where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy.
  - Requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception.
  - The Common Rule agency will determine whether to grant an exception following an assessment of the need.

**Please Note:** FDA does not currently require a single IRB for FDA-regulated cooperative research. However, a proposed rule published 9/28/2022 would harmonize with Common Rule requirements, and an FDA mandate for single IRB will likely go into effect in late 2025/early 2026. [Federal Register :: Institutional Review Boards; Cooperative Research](#)

The Office for Human Research Protections expects that all sites located in the United States participating in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States.

- The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.
- The following research is not subject to this provision:
  - Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe).
  - Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.
  - For research not subject to the above second paragraph, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

All Human Research that falls under social, behavioral, educational, and low-risk biomedical and is conducted by CWRU faculty, staff, and students, falls under the purview of the CWRU IRB.





The CWRU IRB is willing to consider entering into reliance agreements with external IRBs to be a Relying IRB. However, the following steps are required to be completed before submitting to another IRB:

- Permission to use another IRB must be obtained, AND
- An agreement to cede IRB review must be in place, AND
- The faculty member is required to complete and submit a CWRU Reliant Review shell protocol submission via the SpartaIRB system (for review of local requirements).

The CWRU IRB is also willing to serve as the Reviewing IRB for multisite research. Collaboration in advance is required as reliance agreements naming the CWRU IRB as the IRB of record must be in place.

CWRU has entered into reliance agreements with various institutions, as well as with Advarra, an independent central IRB. CWRU and the CWRU IRB has also entered into agreements to participate in the national reliance platform, SMART IRB. The CWRU IRB will continue to consider new opportunities to rely on external IRBs accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

Reliance agreements outline the roles and responsibilities in the reliance relationship between IRBs; however, when using Reliant Review for a research study it is important for investigators to recognize that CWRU and the CWRU IRB still retain important institutional responsibilities for the oversight of the research study. The relying institution must ensure that local ancillary reviews required to conduct Human Research at CWRU are completed and that local requirements and context unique to CWRU are communicated to the IRB of Record.

For assistance with submitting a reliant review study to the CWRU IRB, please reference the Reliant Review Guide located in the Help Center of SpartaIRB: [Reliant Review Guide 06.2019.pdf \(case.edu\)](#)

## What Considerations and Requirements Does CWRU Impose for Reliant Reviews?

Studies will be determined to be eligible for reliant review on a case-by-case basis with consideration given to the type of study, risk level, experience of the Principal Investigator and study team and availability of resources.

Case Western Reserve University will not rely on any IRB that is not accredited by AAHRPP, unless there is a strong justification for relying on the external IRB. These justifications may include federal funding mandate for a single IRB, or if it is required for the collaboration between a CWRU faculty member and their colleague(s) at the external institution.

If the external IRB is not accredited by AAHRPP, a thorough review of the external IRB Policies and Procedures (P&Ps) will be completed by the CWRU HRPP with attention paid to:

- Harmonization with Office for Human Research Protections (OHRP) regulations and guidance;
- Harmonization with Food and Drug Administration (FDA) regulations and guidance;
- Accordance with AAHRPP standards.

The CWRU IRB will document rationale for not relying upon a single IRB review in accordance with NIH policy on exceptions from single IRB review.

## What Are the Steps for the Reliance Request and Acceptance?

Once it is determined that an external IRB will be used for a study and/or there is an agreement to collaborate with an investigator at another institution, the following steps are required by the CWRU Site Principal Investigator (faculty member):

- Obtain a copy of the protocol and consent related document(s).
- Create a CWRU site specific consent document(s) using the template provided by the lead site or sponsor.
- Confirm with the IRB of Record whether or not an IRB Authorization Agreement (IAA) or Collaborating Institutional Investigator Agreement (CIIA) is necessary or if one is already in place.
  - Contact the CWRU HRPP Office for assistance with this step if necessary.
  - There are several different types of reliance agreements.
  - An agreement may cover one study, multiple studies, or all studies at an institution.
  - On rare occasions (on a case-by-case basis), collaborating Institutional Investigator Agreements are also an option when collaborating with an investigator that is not covered by an IRB or FWA.
  - The HRPP Office can help determine if an agreement is needed or if one is already in place.
- Submit a Reliant Review shell protocol Submission to the CWRU IRB via the SpartaIRB electronic system by:
  - Uploading documents received.
  - Access the Reliant Review Guide from the Help Center in the SpartaIRB system (see hyperlink above) for step-by-step instructions on how to create and submit a Reliant Review submission.
- Notify the CWRU HRPP Office by sending an email to [cwru-irb@case.edu](mailto:cwru-irb@case.edu) of requests to rely on external IRBs via the Reliant Review submission.
  - Research studies may not be implemented until the CWRU IRB has provided written notice of acceptance of the request and the IRB of Record has provided written notice of the approval of the study.
  - Investigators must request reliance acceptance from the HRPP Office.
- When requesting to rely on an external IRB, the investigator must submit a Reliant Review Submission, study protocol, and documents related to the informed consent process.
  - CWRU Investigators assume responsibility for engaging research support offices/centers at CWRU with oversight responsibility for the implementation of research and provide any materials needed to those entities in order to grant approval.
  - This includes but is not limited to, department review, Protocol Review and Monitoring Committee, radiation safety, electrical safety, research finance, grants and contracts, etc.
- Upon receipt of the reliance request notification, the CWRU HRPP Office will review the request, will consider protocol specifics and local context and will make a final determination regarding CWRU's willingness to rely on the external institution.
  - The HRPP Office will review the information included with the reliance request to confirm local context/ institutional issues, including personnel qualification, expertise and education requirements, conflict of interests, department approval, required ancillary approval letters, the study protocol and consent documents.
  - When required, the CWRU HRPP Office will also communicate with CWRU's Conflict of Interests Office and the Office of Sponsored Projects regarding any additional requirements related to the study.



- Please note that investigators and study team members are required to complete Conflict of Interests disclosure forms and disclose any COI.
- If a COI management plan has been established by the CWRU COI Committee for the investigator and/or study team member(s), the management plan(s) is/are required to be shared with the HRPP Office to ensure it/they is/are followed pertaining to the new Human Research Study.
- If required, disclosure of the CWRU study team conflict of interests will be disclosed to the reviewing IRB by providing the conflict of interest management plan with site specific documents for review and approval.
- The CWRU HRPP Office will provide an acceptance letter once local requirements have been met. If applicable, a list of suggested revisions, from either the CWRU IRB or from ancillary reviews, will be provided.
- Obtain study approval from the IRB of Record.
  - The CWRU HRPP and IRB Offices are not responsible for the submission to the IRB of Record.
  - The CWRU Investigator and Study Team Members should confer with the lead study team or sponsor to determine the process for submitting to the IRB of Record for the initial review and subsequent reviews.
  - The CWRU PI is ultimately responsible for ensuring that the study has been approved by the IRB of Record before beginning the study at CWRU.
  - The study should not begin at CWRU until the final determination to accept or decline the reliance is communicated by the CWRU IRB and the IRB of Record has approved the study.
  - A study disapproved by the CWRU IRB is not eligible for Reliant Review.

## What Is Required to Ensure the CWRU Site Informed Consent Form Meets the Overall Study and Local Site Requirements?

The CWRU Principal Investigator must collaborate with the lead study team, the IRB of Record and the HRPP Office to create CWRU specific study documents, including the informed consent form.

- If the lead site provides a template consent document, the template must be submitted to the CWRU IRB with the CWRU Reliant Review shell protocol Submission.
- If no template is provided, the CWRU PI should create a site specific consent document or a consent coversheet to be used in conjunction with the main consent document.
- All consent documents should be submitted with the CWRU Reliant Review shell protocol Submission.
- The CWRU IRB will not approve or stamp consent documents, but may, in some situations, provide a list of comments and revisions with the acceptance letter that should be incorporated and/or communicated to the IRB of Record.
- Submission of the final version of the consent to the CWRU HRPP Office is not required and subsequent versions in the event of an amendment are not required to be submitted to the HRPP Office unless otherwise necessary or required.

## What Are the Site PI's Responsibilities for Reporting New Information and Submitting Modifications When Relying on an External IRB as the IRB of Record?

The CWRU Principal Investigator must collaborate with the lead study team and their IRB to complete the following steps:

- Obtain a copy of the reportable event reporting policy of the IRB of Record.
- Over the life of the study, work with IRB of Record via the lead study team on all required subsequent submissions, including modifications, continuing reviews, event reporting, etc.
- Notify the CWRU HRPP Office of any staff changes or changes in Conflicts of Interest by submitting a personnel modification in SpartaIRB.
- Notify the CWRU HRPP Office of any modifications that may alter local approval requirements or the coverage analysis for the study. For example, an additional CT scan would need to be submitted to the Radiation Safety Committee and the coverage analysis team for review.
- Notify the CWRU HRPP Office if the IRB of record makes any determinations of unanticipated problems posing risk to participants or others or any determinations of serious or continuing non-compliance. The CWRU IRB should also be notified of any study suspensions related to risk or non-compliance, any breaches or potential breaches of HIPAA, or other findings directly related to the institutional business of Case Western Reserve University.
  - Consult with the CWRU HRPP Office if you are uncertain whether an event requires dual reporting to the external IRB and the CWRU IRB.
- Notify the CWRU IRB Administration Office once the study is closed. Annual reviews should be submitted to the IRB of record. Work with the lead study team (when applicable) and the IRB of record to provide the required study information and maintain approval of the study. Submission of an annual review form to the CWRU IRB is not required. Once a study is closed, a Notification of Study Closure should be submitted in the electronic record to notify the CWRU IRB of closure.

CWRU HRPP administrators will collaborate as necessary with the IRB of Record for a Reliant Review Study to conduct monitoring visits and compliance reviews, which are designed to identify standards of excellence and potential areas for improvement in order to promote a solid foundation for the conduct of human participants' research.

## What Steps Are Required for the CWRU IRB to Consider Being the IRB of Record for Multi-Site Research?

If planning to conduct multi-site research with the CWRU IRB as the IRB of record, it is recommended that the faculty member contact the HRPP Office **at least 60 days prior to grant submission** or as soon as possible to determine if the CWRU IRB is willing or able to serve as the IRB of record. The HRPP Office needs to review the proposed study and subsites to be involved to determine if the availability of resources are sufficient to provide the necessary oversight of all sites. Any investigators who wish to use the CWRU IRB as the IRB of record for their studies must be aware of their responsibilities as the lead study team:

The Lead Study Team will be the primary point of contact (POC) for communication to and from the Reviewing IRB. Site-specific information from the relying sites will be provided to the lead study team and then submitted to the Reviewing IRB. All communication from the Reviewing IRB will flow from the Reviewing IRB to the Lead Study Team POC to the Relying Study Team POC. This includes (but is not limited to) the following:



- Preparing and submitting the study-wide application for initial IRB review and study-wide modifications to the Reviewing IRB
- Preparing and submitting the site-specific applications and site-specific modifications to the Reviewing IRB that address site variations in study conduct, informed consent language, HIPAA Privacy Rule requirements (if applicable), subject identification and recruitment processes (including recruitment materials), and any other applicable components of the research
- In order to add research sites to previously approved protocols, a modification must be submitted to the CWRU IRB for review and approval. The modification must include the site-specific information, including but not limited to consent forms, conflict of interests management plans, etc. to be used at the relying site. When no significant changes to study procedures are requested / included by the relying site, this may be considered a minor modification that can be reviewed via expedited review.
- If CWRU is responsible for a multi-site research study outside of the United States that is not required to follow requirements for single IRB review, IRB approval must be obtained from international sites and submitted for review by:
  - The CWRU IRB if the study is a low-risk biomedical or social, behavioral or educational Human Research -OR-
  - Another University, Institution, or Central or Commercial IRB if the study falls under a high risk biomedical or clinical trial.
- Providing documentation of IRB determinations to relying site study teams
- Providing copies of IRB-approved materials to the lead study team
- Providing copies of the most current versions of IRB-approved materials to relying site study teams in a timely manner
- Providing the consent form template to relying site study teams
- Providing relevant Reviewing IRB policies to the study teams
- Obtaining and collating study-wide information for continuing review to the Reviewing IRB
- Submitting continuing review progress report to the Reviewing IRB
- Reporting reportable events to the Reviewing IRB (e.g., unanticipated problems, noncompliance, subject complaints)
- Providing the Reviewing IRB with required information when a study is closed.

## What Are Different Types of Reliance Arrangements With Central and Commercial IRBs?

- Central IRB and Commercial IRBs are external IRBs, often for-profit, providing IRB review services.
- CWRU currently has reliance relationships with the Advarra and BRANY IRBs and is willing to consider others as well.

## What Are Reliance Review Platforms?

Several reliance platforms exist to streamline the IRB review process for multisite research relying on a single IRB. Generally, any one institution which has signed on to the platform's agreement may serve as the IRB of Record, but the platform exists as a mechanism to exchange information and/or documents to maintain a robust record of the research study for all sites involved.



***What is the SMART IRB Platform?***

SMART IRB, the Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform, is an electronic system designed to harmonize and streamline the IRB review process for multisite studies, while ensuring a high level of protection for research participants.

Case Western Reserve University is signed on as a participating site for the SMART IRB agreement. The SMART IRB online reliance system is the preferred method for creating and documenting reliance requests.

**What Are IRB Authorization Agreements (IAA)?**

IRB Authorization agreements are agreements executed between an IRB of Record and Relying IRBs outlining the terms and responsibilities of each institution in the reliance relationship. IAAs will be reviewed by the HRPP office and the CWRU Office of General Counsel and signed by the CWRU Institutional Official.

Authorization agreements can be executed for one single study or multiple studies. Investigators interested in collaborating with an institution where the above options are not applicable should contact the IRB for more information about executing an IAA.



## CHAPTER 29 – Requirements for a Prime Awardee of Federally Funded Human Research

### What Are Requirements for a Prime Awardee of Human Research That Is Federally Funded?

The federal regulations require that the prime awardee of federal funding have IRB approval at their institution or a Reliant Review Agreement for their institution to rely on another IRB, even if no Human Research activities are taking place there. Therefore, any time a CWRU researcher is the prime awardee of federal funds, a protocol submission must be submitted in the CWRU SpartaIRB system. This includes either the awardee's IRB (CWRU) to be the IRB of record or a shell protocol for CWRU to rely on an external IRB.

Sometimes it is appropriate to request Overall Approval in these instances:

- Overall Approvals are given for center grants, program grants, and other funding that is awarded without defined protocols for Human Research activities.
- The key is that these grants have funds to support a wide range of activities, some of which may be Human Research and some of which may not.
- ***Please note:*** When the Human Research activities (that are supported by the grant) are fully developed, the individual protocol submission(s) should be submitted via the SpartaIRB system for the CWRU IRB to review and approve or a Reliance Review IRB shell protocol as part of the process for CWRU to rely on an external IRB.
- If your grant does not qualify for overall approval, please contact the Executive Director for the HRPP at [kav6@case.edu](mailto:kav6@case.edu) or 216-368-0134 for a consultation.

## CHAPTER 30 – Requirements for Small Business Innovation Research (SBIR) / Small Business Technology Transfer (STTR) Grant Recipients

### Institutional (Small Business) Engagement in Human Research

- The Office of Human Research Protections (OHRP) is the federal office that oversees HHS-conducted or -supported non-exempt Human Research.
- By regulation, institutions who are engaged in Human Research must have an OHRP approved Federal Wide Assurance and certify IRB review and approval to HHS ([FWAs](#) | [HHS.gov](#))
- OHRP has issued guidance on when institutions are engaged in research.
- OHRP has issued guidance stating that institutions are considered engaged in an HHS-conducted or -supported non-exempt Human Research project when institutions receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt Human Research, even where all activities involving human participants are carried out by employees or agents of another institution.

**In summary**, this means that the Small Business who is the recipient of the SBIR/ STTR grant must apply for and be granted a Federal Wide Assurance AND obtain IRB approval for their role as the prime awardee of the grant.

Case Western Reserve University's Federal Wide Assurance and IRB approval of the research conducted by their faculty, staff, and students DOES NOT extend to the small business and thus DOES NOT fulfill the requirement set by the terms of the award.

### Obtaining A Federal Wide Assurance (FWA)

- All institutions engaged in Human Research that is not exempt from the regulations and is conducted or supported by any HHS agency must be covered by an OHRP-approved assurance of compliance.
- An assurance of compliance is a written document submitted by an institution that is engaged in non-exempt Human Research conducted or supported by HHS in which an institution commits to HHS that it will comply with the requirements set forth in the regulations for the protection of human subjects at 45 CFR part 46.
- The assurance application process must be conducted online by the small business. The assurance application requires that the institution name an IRB.
- This should be the IRB that reviews the largest percentage of the research conducted by the institution covered under the FWA.
- This should NOT be the CWRU IRB. There are a number of independent IRBs that can be named.
- The small business can apply for an FWA here: [eFile](#)
- The FWA must be renewed every 5 years.



**In summary**, the small business will need to apply for and obtain their own Federal Wide Assurance naming the IRB other than the CWRU IRB as they will not be the IRB reviewing the largest part of the businesses research.

## Pre-Grant Submission Information

- For any grant submitted on or after January 25, 2018, a single IRB (sIRB) of record will be used in the ethical review of non-exempt Human Research protocols funded by the NIH that are carried out at more than one site in the United States.
  - SBIR/STTR grants fall under this requirement.
- Beginning January 20, 2020, for federally funded research, any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States.
- The CWRU IRB can act as the IRB of record for social, behavioral, educational, and low-risk biomedical research in a non-hospital setting.
  - This limits the CWRU IRB to be the IRB of record for multi-site research
- If a CWRU faculty member is a Co-Principal Investigator on a SBIR/STTR Grant and the CWRU IRB cannot review the research -AND- another Co-PI on the grant is a faculty member at another University or hospital, then on a case-by-case basis, CWRU may rely on external IRB with a Reliance Review Agreement.
  - Otherwise, the Advarra and BRANY IRBs, independent commercial IRBs, which are fee for service companies, will be required to be the single IRB of record, with a Reliance Review Agreement.
- If a CWRU is a Co-Principal Investigator on a SBIR/STTR Grant and the CWRU cannot review the research and there is not another United States University or hospital involved in the research:
  - The Advarra and BRANY IRBs, independent commercial IRBs, which are fee for service companies, will be required to be the single IRB of record, with a Reliance Review Agreement.
- Please contact the CWRU HRPP Office PRIOR to grant submission to obtain confirmation if the CWRU IRB is able to act as the IRB for the research activities outlined in the grant proposal.
- While a single IRB must review the protocol for both the small business and the CWRU researchers, the CWRU IRB is limited to the type of research activities they can act as the single IRB of record.

**In summary**, if a CWRU faculty member is a Co-Principal Investigator of a SBIR/STTR Grant, on a case-by-case basis, the CWRU IRB may be able to act as the single IRB for research activities that fall under social, behavioral, educational, and low-risk biomedical in a non-hospital setting. Otherwise, another United States University or hospital or Advarra or BRANY IRB, independent commercial IRBs, which are fee for service companies, will be required to be the single IRB of record,

## IRB Protocol Submissions

- If the CWRU IRB is going to act as the IRB of record for the study, CWRU and the small business must enter into an IRB Authorization or Reliance agreement.
- An IRB Authorization or Reliance agreement is an agreement between the small business and CWRU that allows the CWRU IRB to act as the IRB of record for the small business and defines the roles and responsibilities of each party.



- This agreement is needed in ADDITION to the sub-award, and it is managed by the CWRU HRPP Office.
- The CWRU PI should contact the HRPP Office when they are preparing their IRB submission to begin the agreement process.
- This agreement must be kept on file at CWRU and the small business and made available upon request to federal regulatory agencies.
- If CWRU researchers are going to request to rely on an external IRB, they will need to submit an email to the HRPP Office (cwru-irb@case.edu) in order to obtain confirmation that CWRU is agreeable to rely on the particular chosen external IRB.
- If CWRU agrees to rely on the external IRB, the following steps are required before CWRU can rely on the single IRB:
  - The PI is required to submit a Reliance Review (STUDY/SITE) shell protocol via the SpartaIRB system
  - The HRPP Office will be required to establish an IRB Authorization or Reliance Agreement with the chosen external IRB for the specific study.
  - Currently, CWRU uses two independent commercial IRBs: Advarra and BRANY.

**In summary**, fully executed written legal agreements and completion of any corresponding Reliance Review Agreement documents are required for CWRU IRB to act as the IRB for the small business and for CWRU to rely on external IRB.



## CHAPTER 31 – Additional Requirements for DHHS-Regulated Research

*This chapter contains additional considerations for research regulated by the  
Department of Health and Human Services (DHHS)*

1. When a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial should ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent, may continue. The investigator should explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.
2. Investigators are allowed to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the subject's consent, provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. This is the case even if that data includes identifiable private information about the subject.
3. For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, can choose to honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.
4. When seeking the informed consent of participants, investigators should explain whether already collected data about the participants will be retained and analyzed even if the participants choose to withdraw from the research.



## CHAPTER 32 – Additional Requirements for FDA-Regulated Research

*This chapter contains additional considerations for research that is regulated by the  
United States Food and Drug Administration*

### **1. When a subject withdraws from a study:**

- a. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
- b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review and address the maintenance of privacy and confidentiality of the subject's information.
- c. If a subject withdraws from the interventional portion of the study but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.
- d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
- e. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.
- f. Reference [Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials; Guidance for Sponsors, Clinical Investigators, and IRBs](#) for more information.

### **2. For FDA-regulated research involving investigational drugs:**

- a. Investigators must abide by FDA restrictions on promotion of investigational drugs:
  - i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
  - ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
  - iii. An investigator must not commercially distribute or test market an investigational new drug.
  - iv. Reference [CFR - Code of Federal Regulations Title 21 \(fda.gov\)](#) for more information.
- b. Follow FDA requirements for general responsibilities of investigators
  - i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of participants under the investigator's care; and for the control of drugs under investigation.





- ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in [21 CFR §50.23](#) or [§50.24](#) of this chapter.
- iii. Additional specific responsibilities of clinical investigators are set forth in this part and in [21 CFR §50](#) and [21 CFR §56](#).
- iv. Reference [CFR - Code of Federal Regulations Title 21 \(fda.gov\)](#) for more information.
- c. Follow FDA requirements for control of the investigational drug
  - i. An investigator must administer the drug only to participants under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
  - ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
  - iii. Reference [CFR - Code of Federal Regulations Title 21 \(fda.gov\)](#) for more information.
- d. Follow FDA requirements for investigator recordkeeping and record retention
  - i. **Disposition of drug(s)**
    - An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants.
    - If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under [21 CFR §312.59](#).
  - ii. **Case Histories**
    - An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
    - Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.
  - iii. **Record Retention**
    - An investigator must retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
- e. Follow FDA requirements for investigator reports
  - i. **Progress reports:** The investigator must furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
  - ii. **Safety reports:** An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.
  - iii. **Final report:** An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
  - iv. **Financial disclosure reports:**
    - The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under [21 CFR §54](#).



- The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
- f. Follow FDA requirements for assurance of IRB review
  - i. An investigator must assure that an IRB that complies with the requirements set forth in [21 CFR §56](#) will be responsible for the initial and continuing review and approval of the proposed clinical study.
  - ii. The investigator must also assure that they will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human participants or others, and that they will not make any changes in the research without IRB approval except where necessary to eliminate apparent immediate hazards to human participants.
- g. Follow FDA requirements for inspection of investigator's records and reports
  - i. An investigator must upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to [312.62](#).
  - ii. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.
- h. Follow FDA requirements for handling of controlled substances
  - i. If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

**3. For FDA-regulated research involving investigational devices**

- a. General responsibilities of investigators
  - i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of participants under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with [21 CFR §50](#).
- b. Specific responsibilities of investigators
  - i. Awaiting approval: An investigator may determine whether potential participants would be interested in participating in an investigation but must not request the written informed consent of any subject to participate and must not allow any subject to participate before obtaining IRB and FDA approval.
  - ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
  - iii. Supervising device use: An investigator must permit an investigational device to be used only with participants under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
  - iv. Financial disclosure:
    - A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under [21 CFR §54](#).



- The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
- v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:
  - i. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
  - ii. Records of receipt, use or disposition of a device that relate to:
    - The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
    - The names of all persons who received, used, or disposed of each device.
    - Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
  - iii. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. Such records include:
    - Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
    - Documentation that informed consent was obtained prior to participation in the study.
    - All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
    - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy
  - iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
  - v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- d. Inspections
  - i. **Entry and inspection:** A sponsor or an investigator who has authority to grant access must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
  - ii. **Records inspection:** A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, must permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.
  - iii. **Records identifying participants:** An investigator must permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the



- investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
- e. Prepare and submit the following complete, accurate, and timely reports:
- i. **Unanticipated adverse device effects.** An investigator must submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
  - ii. **Withdrawal of IRB approval.** An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
  - iii. **Progress.** An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
  - iv. **Deviations from the investigational plan:**
    - An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of the subject in an emergency.
    - Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
    - Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB also is required.
  - v. **Informed consent.** If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
  - vi. **Final report.** An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
  - vii. **Other.** An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.



## CHAPTER 33 – Additional Requirements For Clinical Trials (ICH-GCP)

*This chapter contains additional requirements for clinical trials under the guidelines for International Conference on Harmonisation (ICH)- Good Clinical Practice (GCP)*

For detailed FDA GCP Guidance, please go to the following website: [E6\(R2\) Good Clinical Practice: Integrated Addendum to ICH E6\(R1\) | FDA](#)

### **Please Note:**

The CWRU IRB complies with ICH GCP guidance (E6) only to the extent that it is compatible with FDA and DHHS regulations. GCP standards contained in the ICH document are not regulatory requirements in the United States.

However, for industry-sponsored studies with contract requirements for institutional adherence to ICH GCP guidance (E6), the CWRU IRB will comply with all of the GCP statements outlined in ICH-GCP guidance (E6), provided that:

- The study team specifically notifies the IRB administration office that the sponsor requires the IRB review process to comply with ICH standards, -AND-
- The Office of Sponsored ProGrants and Contracts office confirms it is a contractual requirement

### **ICH GCP requires the following:**

- Completion of additional training for study team members
- Confirmation that all GCP standards will be followed during the research
- Submission of additional materials and information in IRB to complete the review (PI's CV)
- PI responsibility for reporting requirements, including termination or suspension of the research study by the PI, sponsor, or IRB (see 4.12 of ICH GCP guidance E6)
- Additional elements of informed consent (see 4.8 of ICH GCP guidance E6)

#### ***1. Investigator's Qualifications and Agreements***

- The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable regulatory requirements.
- The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities.
- The investigator should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.
- The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
- The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
- The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.



## **2. Adequate Resources**

- The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable participants within the agreed recruitment period.
- The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.

## **3. Medical Care of Trial Participants**

- A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
- During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.
- It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
- Although a subject is not obliged to give their reasons for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights.

## **4. Communication with IRB**

- Before initiating a trial, the investigator/institution should have written and dated approval opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to participants.
- As part of the investigator's/institution's written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB.
- During the trial the investigator/institution should provide to the IRB all documents subject to review.

## **5. Compliance with Protocol**

- The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities and which was given approval opinion by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
- The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to trial participants, or when the changes involves only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).





- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial participants without prior IRB approval opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendments should be submitted: a) to the IRB for review and approval opinion, b) to the sponsor for agreement and, if required, c) to the regulatory authorities.

## **6. *Investigational Product***

- Responsibility for investigational product accountability at the trial site rests with the investigator/institution.
- Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
- The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
- The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
- The investigator should ensure that the investigational product are used only in accordance with the approved protocol.
- The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
- Randomization Procedures and Unblinding: The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.

## **7. *Informed Consent of Trial Participants***

- In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval opinion of the written informed consent form and any other written information to be provided to participants.
- The written informed consent form and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that



may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

- Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
- None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
- The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
- The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
- Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
- Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
- If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participants, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
- Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following:
  - That the trial involves research.
  - The purpose of the trial.
  - The trial treatments and the probability for random assignment to each treatment.
  - The trial procedures to be followed, including all invasive procedures.
  - The subject's responsibilities.
  - Those aspects of the trial that are experimental.
  - The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
  - The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
  - The alternative procedures or courses of treatment that may be available to the subject, and their important potential benefits and risks.



- The compensation and/or treatment available to the subject in the event of trial related injury.
- The anticipated prorated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, to the subject for participating in the trial.
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- The persons to contact for further information regarding the trial and the rights of trial participants, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- The expected duration of the subject's participation in the trial.
- The approximate number of participants involved in the trial.
- Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the participants. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to participants.
- When a clinical trial (therapeutic or non-therapeutic) includes participants who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
- Except as described above, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in participants who personally give consent and who sign and date the written informed consent form.
- Non-therapeutic trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled: a) The objectives of the trial cannot be met by means of a trial in participants who can give informed consent personally. b) The foreseeable risks to the participants are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval opinion of the IRB is expressly sought on the inclusion of such participants, and the written approval opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
- In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of



the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

## **8. *Records and Reports***

- The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
- Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.
- The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
- Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
- The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
- Upon request of the monitor, auditor, IRB, or regulatory authority, the
- investigator/institution should make available for direct access all requested trial-related records.

## **9. *Progress Reports***

- The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.
- The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to participants.

## **10. *Safety Reporting***

- All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers



assigned to the trial participants rather than by the participants' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB.

- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
- Premature Termination or Suspension of a Trial If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants, should assure appropriate therapy and follow-up for the participants, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:
  - If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
  - If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
  - If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

### ***11. Final Reports by Investigator***

- Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.





## CHAPTER 34 – Department of Defense Research

*This chapter includes additional requirements for research regulated  
by the Department of Defense (DOD)*

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
3. Employees of the Department of Defense (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the Department of Defense cannot be paid for conducting research while on active duty.
4. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human participants while on-duty or off-duty.
5. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
6. There may be specific educational requirements or certification required.
7. When assessing whether to support or collaborate with this institution for research involving human participants, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
8. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
  - Prohibit an individual from receiving pay of compensation for research during duty hours.
  - An individual may be compensated for research if the participant is involved in the research when not on duty.
  - Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
  - Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
9. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
10. Other specific requirements of the Department of Defense research can be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the IRB's "WORKSHEET: Additional Federal Criteria (HRP-318)" here:  
<https://spartairb.case.edu/IRB/sd/Doc/0/S0OLBO3GGVRKD0EK0G893UMK37/HRP-318%20-%20WORKSHEET%20-%20Additional%20Federal%20Agency%20Criteria.docx>





## CHAPTER 35 – Department of Justice Research

*This chapter includes additional requirements for research regulated by the Department of Justice (DOJ)*

### Additional Requirements for DOJ Research Conducted in the Federal Bureau of Prisons

1. Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.
2. The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
3. The research design must be compatible with both the operation of prison facilities and protection of human participants.
4. Investigators must observe the rules of the institution or office in which the research is conducted.
5. Any investigator who is a non-employee of the Bureau of Prisons must sign a statement in which the investigator agrees to adhere to the requirements of [28 CFR §512](#).
6. The research must be reviewed and approved by the Bureau Research Review Board.
7. Incentives cannot be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the test setting may be offered. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both: No longer in Bureau of Prisons custody. Participating in authorized research being conducted by Bureau employees or contractors.
8. A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as statistical research or reporting record is provided to the agency.
9. Except as noted in the consent statement to the subject, you must not provide research information that identifies a subject to any person without that subject's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.
10. Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
11. If you are conducting a study of special interest to the Office of Research and Evaluation but the study is not a joint project involving Office of Research and Evaluation, you may be asked to provide Office of Research and Evaluation with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.
12. Required elements of disclosure additionally include:
  - Identification of the investigators.
  - Anticipated uses of the results of the research.
  - A statement that participation is completely voluntary and that the subject may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
  - A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, an investigator may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or



- harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.
- A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.
13. You must have academic preparation or experience in the area of study of the proposed research.
  14. The IRB application must include a summary statement, which includes:
    - Names and current affiliations of the investigators.
    - Title of the study.
    - Purpose of the study.
    - Location of the study.
    - Methods to be employed.
    - Anticipated results.
    - Duration of the study.
    - Number of participants (staff or inmates) required, and amount of time required from each.
    - Indication of risk or discomfort involved as a result of participation.
  15. The IRB application must include a comprehensive statement, which includes:
    - Review of related literature.
    - Detailed description of the research method.
    - Significance of anticipated results and their contribution to the advancement of knowledge.
    - Specific resources required from the Bureau of Prisons.
    - Description of all possible risks, discomforts, and benefits to individual participants or a class of participants, and a discussion of the likelihood that the risks and discomforts will actually occur.
    - Description of steps taken to minimize any risks.
    - Description of physical or administrative procedures to be followed to: Ensure the security of any individually identifiable data that are being collected for the study.
    - Destroy research records or remove individual identifiers from those records when the research has been completed.
    - Description of any anticipated effects of the research study on institutional programs and operations.
    - Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
  16. The IRB application must include a statement regarding assurances and certification required by federal regulations, if applicable.
  17. You must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor.
  18. At least once a year, you must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
  19. At least 12 working days before any report of findings is to be released, you must distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance.
  20. You must include an abstract in the report of findings.
  21. In any publication of results, you must acknowledge the Bureau's participation in the research project.
  22. You must expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
  23. Prior to submitting the results of a research project conducted under this subpart for publication you must provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.



24. Other specific requirements of the Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons (BOP) can be found in the “Additional Requirements for Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons “(BOP)” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

## Additional Requirements for DOJ Research Funded by the National Institute of Justice

1. The project must have a privacy certificate approved by the National Institute of Justice Human Participants Protection Officer.
2. All investigators and research staff are required to sign employee confidentiality statements, which are maintained by the responsible investigator.
3. The confidentiality statement on the consent document must state that confidentiality can only be broken if the subject reports immediate harm to participants or others.
4. Under a privacy certificate, investigators and research staff do not have to report child abuse unless the subject signs another consent document to allow child abuse reporting.
5. A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.
  - At least once a year, the researcher shall provide the Executive Director for the Human Research Protection Program with a report of the progress of the research.
  - At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
  - In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
  - The research shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
  - Prior to submitting for publication, the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Executive Director for Human Research Protections, and Bureau of Prisons
6. Other specific requirements of the Department of Justice (DOJ) Research Funded by the National Institute of Justice can be found in the “Additional Requirements for Department of Justice (DOJ) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”



## CHAPTER 36 – Department of Education Research

*This chapter includes additional requirements for research regulated  
by the Department of Education (ED)*

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children involved in the research must be able to inspect these materials.
3. The school in which the research is being conducted must have policies regarding the administration of physical examinations or screenings that the school may administer to students.
4. Other specific requirements of the Department of Education (ED) Research can be found in the “Additional Requirements for Department of Education (ED) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”



## CHAPTER 37 – GDPR Requirements

This chapter contains additional requirements for research subject to the European Union (EU) General Data Protection Regulations (GDPR)

1. Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to [EU General Data Protection Regulations](#).
2. For all prospective Human Research subject to EU GDPR, contact CWRU's Office of General Counsel or the Compliance Officer to ensure that the following elements of the research are consistent with institutional policies and interpretations of EU GDPR:
  - Any applicable study design elements related to data security measures.
  - Any applicable procedures related to the rights to access, rectification, and erasure of data.
  - Procedures related to broad/unspecified future use consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.
3. Where FDA or DHHS regulations apply in addition to EU GDPR regulations, ensure that procedures related to withdrawal from the research, as well as procedures for managing data and biospecimens associated with the research remain consistent with the corresponding Chapters in this Investigator Manual.

## CHAPTER 38 – Preparedness Considerations For An Emergency or Disaster

Investigators conducting human research should be aware of unplanned events or disasters (e.g., extreme weather events, natural disasters, man-made disasters, infectious disease pandemics, etc.) that may disrupt typical research. Therefore, the following additional considerations are associated with managing Human Research during an emergency/disaster scenario related to investigators' ongoing interactions with research participants and the Institutional Review Board (IRB) in such cases.

### Consider Different Types of Emergencies/Disasters

Emergencies may include natural or human-made disasters and can vary in the length of time and severity of their existence. Different types of emergencies will require different responses and responses to an emergency may change depending on the research state and the types of activities being conducted.

Please consider your research at its various stages with the following situations:

- Suspension of activities lasting one week versus one month (or longer)
- Suspension of in-person engagement in favor of online activities
- Limited versus lack of access to physical research spaces such as labs or offices
- Operating with limited research staff or resources
- Working with distressed research populations
- Engaging in face-to-face communication versus mediated communication (over the phone, via Zoom, etc.)
- Participants' lack of technology, unreliable WIFI, or limited resources

### Deciding Whether a Study-Specific Risk Mitigation Plan for Ongoing Research Is Needed

In general, investigators should develop a study-specific emergency/disaster risk mitigation plan for their research unless one of the following is true:

- Research does not involve in-person interaction with research participants.
- Research can be conducted as written while adhering to additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event.
- The research is externally sponsored, and the sponsor has developed a protocol-specific risk mitigation plan for the research.
- The research has been voluntarily placed on hold for recruitment and all research procedures (except for necessary follow-up procedures to be done consistently with additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event).

### Tools and Resources for Developing Study-Specific Emergency/Disaster Risk Mitigation Plans for Ongoing Research

- Review “HRP-108 - FLOWCHART - Study-Specific Emergency-Disaster Risk Mitigation Planning” and



- “HRP-351 - WORKSHEET - Protocol-Specific Emergency-Disaster Risk Mitigation Plan”

## Voluntary Holds on Human Research Activities

Investigators may voluntarily elect to place all recruitment, enrollment and research procedures on temporary hold during emergency/disaster scenarios if doing so will better ensure the safety of research participants and would not create any additional risks to the safety and welfare of research participants. Such voluntary holds on research activity do not require IRB notification or review.

## Submitting Study-Specific Emergency/Disaster Risk Mitigation Plans for IRB Review

- If immediate modification of the research is necessary to eliminate an apparent immediate hazard to a subject, take action and notify the IRB within five business days following the standard pathway to submit reportable new information.
- For all other study modifications made to ensure the ongoing safety of research participants during emergency/disaster scenarios, submit a study amendment and all relevant new or modified study materials to the IRB.

## Other Reportable New Information Considerations During Emergency/Disaster Scenarios

- The IRB’s list of reportable events includes two items for which additional clarification and guidance may be helpful during emergency/disaster scenarios.
  - “Failure to follow the protocol due to the action or inaction of the investigator or research staff.”
    - Emphasis on action or inaction of the investigator or research staff has been added because this requirement does not include action or inaction of the research subject.
    - For example, study teams may notice an increase in the number of participants who do not arrive for scheduled research visits under emergency/disaster circumstances.
    - Failure of a research participant to appear for a scheduled research visit is not noncompliance due to action or inaction by the investigator or research staff, and therefore does not require reporting to the IRB.
  - “Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.”
    - During emergency/disaster scenarios, there will be cases where there is sufficient time to receive IRB approval of any proposed modifications to previously approved research, and in such cases, investigators should follow standard IRB procedures for submitting modifications.
    - However, there will be other cases where investigators must make more immediate changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants.
    - Such changes may be implemented without IRB approval but are required to be reported to the IRB within five business days afterward in accordance with IRB policies and procedures for submitting reportable new information.

## APPENDIX A – Certificate of Confidentiality

A Certificate of Confidentiality (see [Certificates of Confidentiality \(CoC\) | Grants & Funding \(nih.gov\)](#)) is issued to protect participants' privacy and ensure the confidentiality of their data. The Certificate prevents researchers from having to release identifying information about human research participants in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings, or to any other person not connected with the research. This protection is afforded by the Public Health Service Act 301(d), 42 USC 241(d) [Certificates of Confidentiality - Privacy Protection for Research Subjects: OHRP Guidance \(2003\) | HHS.gov](#).

### When Is a Certificate Issued, and What Does It Protect?

#### *NIH Funded Studies*

The NIH will issue Certificates of Confidentiality to any person engaged or intending to engage in research that will collect identifiable, sensitive information. The Certificates will be included in the NIH Grants Policy statement as a standard term and condition of the award effective October 1, 2017 for new and non-competing awards. Institutions and investigators are responsible for determining whether their research includes the collection or use of identifiable, sensitive information and are therefore required to protect the privacy of individuals who are participants of such research.

This includes:

- Human subjects research as defined in the Federal Policy for the Protection of Human Subjects ([45 CFR 46 | HHS.gov](#)), including exempt research.
  - Exception: Human Research that is exempt from all or some of the requirements of 45 CFR 46 if the information obtained is recorded in a manner that the participants cannot be identified or readily ascertained, directly or through identifiers linked to the participants.
- Research involving the collection or use of biospecimens that are identifiable.
- Research involving the generation of individual level human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in a manner that participants can be identified.
- Research that involves biospecimens or information about an individual where there is a risk that the identity of an individual could be deduced from some combination of the specimen/information, a request for the specimen/information, or other available data sources.

Sensitive information can include (but is not restricted to):

- Information regarding the use of alcohol, illegal drugs or other addictive products.
- Information concerning illegal behavior.
- Information that can be destructive to the subject's financial standing, employability or reputation within the community or might lead to social disgrace or prejudice.
- Information regarding the subject's psychological state or mental health.

The Certificates for NIH funded studies protect a subject's information that was collected or used during the period in which the research is funded by NIH. This information, and all copies thereof, is protected by a Certificate in perpetuity, even after the research is no longer funded by NIH. Investigators are responsible for informing secondary researchers when information disclosed to them is protected by a Certificate. If the



study continues after the NIH funding ends and new information will be collected and used, the investigator should apply for a certificate following the process for non-NIH funded research.

### ***Non-NIH Funded Studies***

Any person engaged or intending to engage in non-NIH funded research that will collect identifiable, sensitive information should apply for a Certificate.

A Certificate for non-NIH funded studies protects a subject's information collected for a distinct period of time (the duration of the study). If a study's duration needs to be extended, and data collection will continue past the expiration date of the Certificate, the researcher must submit a written request to the appropriate agency for an extension of the Certificate expiration date. NIH and other agencies request that this proposal be submitted at least 3 months prior to the expiration date. Extension applications should consist of why the researcher needs the extension, an estimated time as to how long the extension will be, most recent IRB approval of the protocol, and the copy of the consent form which states a Certificate has been obtained. Any information collected outside the approval period of the certificate is not protected. However, the information that was collected during the time the Certificate was valid is protected indefinitely.

### ***How to Apply for a Certificate for non-NIH funded studies***

Applications should be made after the IRB has reviewed and approved the protocol. Certificates of Confidentiality are issued by agencies within the Department of Health and Human Services (such as the Centers for Disease Control and Prevention, Food and Drug Administration, or National Institutes of Health), and researchers should apply to the particular agency involved in the funding or regulation of the study, or to the NIH Institute or Center that funds research in a scientific area similar to your project. **Please contact the HRPP Office to help in this process.** The Research Compliance Officer, Kim Volarcik (kav6@cas.edu) should be contacted and will need to sign-off in order to submit the request.

### ***How do Certificates apply to Multi-center Trials?***

For multi-site protocols, the coordinating center of non-NIH funded research may apply for a Certificate to cover all sites. The coordinating institution must have the IRB approvals from all sites available upon request for the NIH. All consent forms from all sites should state the correct language regarding the Certificate.

## **IRB Requirements Relating to Certificates of Confidentiality**

NIH funded studies that include the collection or use of identifiable, sensitive information must add language to the informed consent document that states that the research is covered by a Certificate of Confidentiality, explain the protections offered by the Certificate, and any limitation to these protections. Suggested text can be found in the CWRU informed consent templates for social behavioral and biomedical research found in the Library tab at <https://spartairb.case.edu/>

Researchers planning to collect sensitive information for non-NIH funded studies must obtain a Certificate of Confidentiality. Once local IRB approval has been obtained, with language in the informed consent document that notes a Certificate of Confidentiality will be obtained for the project, the researcher can apply for a new Certificate via NIH or other funding agencies website. Once a Certificate is obtained, the researcher should modify the local IRB protocol application and informed consent documents to state that a Certificate of Confidentiality has been acquired.

# APPENDIX B – Ensuring Comprehension During the Informed Consent Process

## Overview

It is the Principal Investigator and study team members' ethical responsibility in research to disclose information to a potential research participant and to ensure that the person has the capacity to reach a decision based on the information provided. Obtaining valid informed consent is a necessary component in the research process.

For participation in a study to be truly voluntary, the participants must understand what they are agreeing to do. The researcher must present the information to the participant in a way that is understandable to participants, and then assess whether the participant did, indeed, understand the information. The researcher must make sure that the participant understands all the important elements of the consent form at the time consent is obtained and during the research study. The participant must understand that participation is voluntary and that they can withdraw from the study at any time.

Regardless of a potential research participant's literacy level, it is important that researchers ensure that they understand the information that has been given to them about the research study. Literacy level is comprised of "the degree to which an individual has the capacity to obtain, communicate, process, and understand basic information to make appropriate decisions." All participants should not feel rushed.

### ***1. Ways to present information on the informed consent form (ICF) to improve readability:***

- Write at or below an 8th grade reading level
- Use short sentences; < 15 words
- Use the active form (first person)
- Use 12-point font
- Avoid jargon and acronyms; define medical terms
- Format information to improve visual understanding by using:
  - Tables
  - Bulleted lists
  - White space
- Provide information in a question-and-answer format. This format is particularly useful when the study procedures are complex, and/or the target subject population has a below average education or reading level

### ***2. Assess readability of ICF before submitting for IRB approval:***

- Use online indices:
  - Flesch-Kincaid Grade Level Index. This test is automatically calculated on your Microsoft Word documents. After Microsoft Word completes a grammar check (under tools in the tool bar), readability statistics are displayed.
  - Flesch-Kincaid Grade Level Score indicate the years of education required for a person to understand the text.
  - Flesch-Kincaid Reading Ease-Higher number is better. Aim for >80.
- Ask someone not on your research team to read through the consent document and provide feedback



### 3. *Assess Participant Comprehension:*

- The responsibility of ensuring that a potential participant understands the research and the risks and benefits involved falls upon the researcher and not upon the potential participant.

Employ the Teach-back method during the informed consent process for Expedited and Full Board Review protocols. It is critical to the consent process that the researcher not only field questions but also asks questions.

- Asking questions can further the discussion, elicit questions from the potential participant, prompt the potential participant to think more carefully about the study, and help the researcher decide whether the person has adequately understood the study.
- The Teach-back method is a strategy to improve the researcher's ability to explain the ICF content in a clear way.
  - It assures that the prospective participant is provided with sufficient opportunity to discuss the information provided to them and to consider whether to participate in the research.
  - It involves asking potential research participants to demonstrate understanding (i.e., how well you explained it to them), using their own words and using open-ended or non-directive questions (i.e., questions that begin with who, what, when, how or please describe) as opposed to close-ended questions that simply elicit a yes/no response.
- Teach-back questions are a way to check understanding by asking participants to state in their own words what the research study is about and what they will be expected to do if they chose to participate.

## Suggested Open-Ended Questions

For studies obtaining in-person or remote consent, select a minimum of 3 open-ended questions that will be asked during the consent process to ensure research participant comprehension:

- In your own words, could you please tell me what you will be doing during this study?
- Can you tell me the purpose of this study?
- Can you tell me what will happen if you agree to take part in this study?
- Can you tell me what drawbacks might be to taking part in this study?
- How might this study help you or others?
- What would you do if you wanted to leave the study?
- What will happen if you decide not to be in the study?
- What are the consequences if you withdraw from the study?
- What more would you like to know?

## **What if the participant could not successfully explain the research study components?**

When the research is being conducted face-to-face, there is opportunity for the researcher to re-phrase the information if the participant was not able to repeat the information accurately. Re-explain if the participant is not able to repeat the information accurately. Try to explain in different words or use another analogy.

Ask the patient to teach back the information again, using their own words, until you are confident that they really understand the components of the study. If they still do not understand, consider other strategies.

Assess appropriateness of consenting them to the study.

Here are additional suggestions:

- Be encouraging
- Do say:
  - “I am sorry I did not explain it well enough.”
  - Paraphrase the part they struggled with.
  - “Could you tell me in your own words what that means you will be doing?”

## Employ Consent Quizzes for Online Studies

Electronic comprehension checks (quizzes) interspersed throughout or at the end of a consent document may be used to assess comprehension prior to a participant's entrance into a study site or prior to engaging in any research activities. Participants must score a certain level of accuracy on their comprehension checks to be eligible for the research (e.g., 2 out of 3 questions answered accurately). Consider providing the correct answer for any questions missed and allowing the participant to re-take the missed item or answer an alternate item accurately before being allowed to proceed. For those who do not meet these criteria indicate they may contact the Principal Investigator for assistance.

Select a minimum of three questions asked on the consent form to assess subject comprehension prior to being able to proceed with online research procedures. These may be in the form of a closed response option (e.g., Yes/No, True/False) or multiple-choice format.

- What is the purpose of this study? (provide multiple choice options)
- What will happen if you agree to take part in this study? (provide multiple choice options)
- Do you have to be in this study? (Yes/No)
- There are no risks to being in this study (True/False)

Please contact Utech if you have questions or need help in implementing the questions in your electronic informed consent form.

## Determine Eligibility

If it is determined that the potential participant adequately understands the study information in the ICF, the study team may enroll the participant.

If it is determined that the potential participant does not understand or have the capacity to provide informed consent, the researcher must either exclude the potential participant from enrollment to the study or seek surrogate consent for participation. Inclusion of a legally authorized representative for the use of surrogate consent requires submission of a protocol modification for review and determination by the IRB. Please see Chapter 18 – Decisionally Impaired Persons.

## When Including Children in Research

For studies with children, the assent process should include at least 2 open-ended questions.

## Resources

Dartmouth's Teach Back resource program: [Teach Back \(dartmouth.edu\)](https://teachback.dartmouth.edu)

For resources on Literacy: [Health Literacy and the IRB](#) | [Health Literacy Studies](#) | [Harvard T.H. Chan School of Public Health](#)



## APPENDIX C – CWRU Research Participant Payment Guidance

This appendix summarizes information found in the CWRU Procurement document CWRU Research Participant Payment Guidance. **For the full guidance, see: [CWRU Research Participant Payment Guidance Update Rv Dec 2023.pdf \(case.edu\)](#)**

### List of Payment Methods

The chart below contains a list of payment methods, the type of participant, and scenarios where the method would be most appropriate to use.

Internal Participant: Any person on payroll, and/or students with an active status.

External Participant: Persons not on CWRU payroll nor active students.

Type of Payment Method	Type of Research Participant	Recommended Usage
PNC ePayments (preferred method)	External	One time or multiple payments, all types of interactions
Gift Card – Physical Card	External and Internal	Known finite group of participants, One to two payments, when anonymity is required, when interaction is face to face and payment is expected at time of participation
Gift Card – Electronic	External and Internal	Known finite group of participants, One to two payments per participant, when group of participants have access to email, cell phone and or computer, all types of interaction.
Payment Requests	External	Recommended when payment to volunteer is a one-time payment of \$250 or more, when you know that the volunteer will be paid more than \$599 for participation per year in multiple payments
Venmo/PayPal or other Cash Apps	External	Only to be used in specific situations that are approved by Research Administration and Procurement
Petty Cash	External	Last resort – only recommended when no other method will work

Please see [CWRU Research Participant Payment Guidance Update Rv Dec 2023.pdf \(case.edu\)](#) for information regarding procurement procedures and contacts.

### IRS Information

Per the Internal Revenue Service (the IRS), cash and cash equivalents, such as gift cards, have a readily ascertainable value. They are taxable income regardless of the face amount. For employees, all gift cards (and any gifts) are considered compensation and are subject to federal, state, and employment tax withholding and reporting on Form W-2 via completion and submission of this form via payroll@case.edu. There is no minimum dollar amount for this rule.

For non-employees, the value of all gifts and gift cards/debit cards in an aggregate amount of \$600 or more across campus, per calendar year must be reported to the IRS on Form 1099-MISC as other compensation. Therefore, it is necessary to collect the payee's unique taxpayer ID (SSN) in order to report cumulative payments in excess of \$600 per calendar year.

Finally, gift cards/debit cards given to nonresident aliens are subject to federal tax withholding. All IRB submissions and consent forms shall include language to address the collection of this data.

Departments purchasing and distributing gift cards are responsible for compliance with IRS regulations and university policies. Note that unused gift cards cannot be returned.

# APPENDIX D – Guidance for the Transfer of Whole Genome Sequencing Data to CWRU

## Definitions Pertinent to Whole Genome Sequencing Data

**DNA sequencing** represents a collection of methods that assay or determine the exact order of the bases along a strand of DNA.

**Gene** is a sequence of nucleotides in DNA or RNA that codes for a molecule that has a function. It is also described as a unit of heredity transmitted from parent to offspring that results in an observable characteristic in the offspring.

**Genome** is often described as the whole hereditary information of an organism that is encoded with DNA. It is the complete DNA sequence of an organism that includes all of its genes and the DNA between genes.

**Genomics** is the characterization, quantification, and interaction of how all genes influence the biology of an organism.

**Whole-genome Sequencing (WGS)** is one of several techniques used in Genomic Research for assays analyzing entire genomes. Humans are diploid (22 pairs of autosomes and a pair of sex chromosomes), and the human genome is approximately 3 billion base pairs. WGS only targets DNA that is known to code for genes and has the potential to identify novel variants. WGS is the method of choice for undiagnosed rare disorders. It is also truly genome-wide and is used in population-scale genomic discovery studies like whole genome genotyping albeit still less frequently given the expense.

## Overview

CWRU recognizes the importance that whole genomic data (WGS) plays in the conduct of biomedical research by CWRU researchers. This data is extremely useful in both the scientific and medical arenas. The purpose of this guidance document is to identify the process required so that CWRU researchers may receive and store WGS data for research purposes from other institutions and agencies. This process is jointly managed by the Office of Research Administration Data Use Agreement Office as well as the Institutional Review Board.

WGS is transferred without any personal identifiers in large batches of multiple files and in most cases according to standard formats and vocabularies/ontologies. The identity of the individuals within the data sets cannot be readily ascertained. It has been noted that the risk of re-identification of a person based on WGS is very low. Re-identification of individuals using whole genomic sequencing data requires extensive knowledge of omic data analysis and specialized software or hardware. WGS data stored as VCFs cannot be opened by Microsoft Word, Excel, or Notepad but instead require specific software. Other WGS files such as FASTQ and BAM will require terabytes of storage space depending on the sample size of the study.

## Guidance

1. Researchers interested in receiving WGS for research purposes from any source outside the institution must complete a DUA Request form. The form and detailed instructions for completing the form are on the following website: <https://case.edu/research/faculty-staff/technology-transfer/material-transfer-data-use-agreements>.
2. The DUA request is reviewed by the DUA team and a draft agreement is obtained from the sending party.
3. The DUA team reviews the draft agreement and the DUA request form focusing particularly on:
  - a. The purpose of the research and it is benefited by the transfer of GWS data and the population from whom the data was collected.
  - b. The researcher's role on the project.
  - c. The data provider and their relationship to the CWRU researcher.
  - d. The terms and conditions of the agreement. Do the terms:
    - i. Specifically prohibit the attempt to identify individuals from whom the data was collected.
    - ii. Require IRB approval.
    - iii. Have data storage and physical transfer requirements.
4. The DUA team evaluation will determine:
  - a. Whether or not IRB approval is required.
    - i. IRB approval will be required for any of the below circumstances:
      - The DUA terms and conditions require IRB approval.
      - The DUA terms and conditions do not explicitly prohibit the attempt to use the data to identify individuals.
      - If the researcher is engaged in the research of the project and as a result could gain access to the identifiers.
      - If the data is from a vulnerable population.
    - ii. IRB approval will be required if the researcher is engaged in the research.
  - b. If the plan for storage of the data fits the requirements of the agreement.
5. If IRB approval is required, then the researchers will be informed they must submit an IRB protocol for review and approval through the IRB system located at <https://spartairb.case.edu/>
6. The DUA team will negotiate and execute the agreement after:
  - a. Data security has been ensured and
  - b. The IRB has:
    - i. Made a determination that the protocol falls under not human research or exempt research, or
    - ii. Approved the non-exempt protocol