IRB Handbook for Investigators, Institutions, Sponsors, and Sponsors' Representatives

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FDA/OHRP IRB Registration Number: IRB00000971

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1. Introduction

1.1. Regulatory Changes (Common Rule Changes Effective January 21, 2019)

The Advarra IRB Handbook has been updated to include the Common Rule changes effective on January 21, 2019 (the "Compliance Date"). The Department of Health and Human Services (HHS) issued revisions to the Federal Policy for the Protection of Human Subjects (also known as the "Common Rule"), which apply to human subject research conducted or supported by DHHS and other federal agencies that adopted the Common Rule. The Common Rule changes have been accepted by all agencies that have adopted the Common Rule except the Department of Justice. Human subject research conducted or supported by each federal department/agency is governed by the regulations of that department/agency.

In this Handbook, we refer to the Common Rule in effect **before** January 21, 2019 as the "Old Common Rule" and the Common Rule in effect **on and after** January 21, 2019 as the "Revised Common Rule." The Revised Common Rule applies to studies that must comply with the Common Rule and are approved on or after the Compliance Date. Studies approved prior to the Compliance Date are not required to comply with the Revised Common Rule.

Studies conducted under FDA regulations only are not required to comply with the Common Rule, but studies subject to both the Common Rule and FDA regulations must comply with both sets of regulations. Within this Handbook, we will provide information about different requirements under the Old Common Rule and Revised Common Rule where applicable.

Advarra applies (1) the FDA regulations to FDA-regulated research; (2) the Revised Common Rule to federally funded research approved on or after the Compliance Date (with the exception of the Department of Justice) and exemption requests submitted after the Compliance Date; and (3) the Old Common Rule to federally funded research approved prior to the Compliance Date, non-federally funded research that is not FDA-regulated, and research funded by the Department of Justice.

1.2. Purpose of Handbook

The purpose of the Advarra IRB Handbook for Investigators, Institutions, Sponsors, and Sponsors' Representatives is to orient investigators, research staff, sponsors, contract research organizations (CROs), and site management organizations (SMOs) to the IRB's policies, procedures, guidelines, and expectations. The Handbook includes information related to the initial review process through management of ongoing research activities and study closure. To comply with conditions of IRB approval, the policies, procedures, and guidelines outlined in this document must be followed during the conduct of a research study to ensure adequate protection for the rights and welfare of research subjects.

Please note "sponsor" is referenced throughout the Handbook. The term "sponsor" also applies to CROs and SMOs acting on a sponsor's behalf.

Revisions to the IRB Handbook will be made on an as-needed basis to reflect changes in the IRB's policies and procedures and/or federal regulations and guidance documents. Any changes to the Handbook are communicated via the IRB's cloud-based Advarra CIRBI Platform (www.cirbi.net) and will always be posted in the Reference Materials section of CIRBI for immediate access.

Note: *This document uses hyperlinks to help users quickly access external, web-based resources for more information. The table of contents is also hyperlinked for direct navigation to relevant sections. Some of our clients keep a printed copy as a desk-side reference; however, we suggest keeping an electronic version so the embedded links are accessible. The embedded links are validated with each new version. If a link is not working as anticipated, please contact* info@advarra.com.

1.3. Scope of Services

The IRB reviews all phases of research involving the use of drugs, biologics, devices, pesticides, as well as expanded access protocols (often call "compassionate use"), and humanitarian use devices (HUDs). In addition, the IRB reviews consumer product and behavioral and social science research and also makes formal determinations as to whether activities constitute human subject research and if such activities are exempt from IRB requirements.

The IRB reviews protocols for sites in all 50 US states and territories as well as in most Canadian provinces. In addition, the IRB reviews international research to help ensure compliance under ICH GCP and US federal regulations (if applicable).

The IRB reviews research studies conducted by a single investigator or multiple investigators. Regardless of the number of investigators conducting the research, the IRB keeps each sponsor (for multisite research) and investigator/site informed of actions that occur during the conduct of the study and will provide written notification of the IRB's actions/determinations and requirements.

In addition to IRB services, Advarra offers institutional biosafety (IBC) review and support services as well as global research compliance consulting services.

1.4. OHRP/FDA IRB Registration

Advarra is registered with OHRP and FDA under registration number IRB00000971. The IRB's registration number can also be confirmed at http://ohrp.cit.nih.gov/search/. For more information, see 1.5 Statement of Compliance.

1.5. IRB Composition/Membership

Advarra has 1 review board with primary and alternate members. Members are categorized as (1) physician-scientist, (2) other-scientist, or (3) non-scientist. Any non-scientist alternate member can serve as a voting alternate for a primary non-scientist. Any physician-scientist can serve as a voting alternate for a primary physician-scientist **or** other-scientist. Any other-scientist can serve as a voting alternate for a primary other-scientist.

Although fully supported operationally and administratively, the IRB's deliberative processes and regulatory actions are independent from all other components of Advarra.

The IRB's membership includes individuals who have professional experience, knowledge, and expertise to review human subjects research. On occasion, the IRB requests the assistance of a consultant with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB.

The IRB's current membership roster is available in CIRBI under Reference Materials. Any changes to the roster are updated on the site and communicated to client contacts via CIRBI.

Advarra policies prohibit IRB members from reviewing research with which they have potential conflicts of interest. In their contracts, all IRB members agree to disclose potential conflicts and not to participate in impacted research reviews. Additionally, the IRB meeting chairperson and IRB staff remind IRB members of this obligation at the beginning of every meeting and determine whether IRB members must recuse themselves due to potential conflicts.

1.6. Statement of Compliance

Advarra is organized and operates in compliance with the US federal regulations (including but not limited to 21 CFR Parts 50 and 56 and 45 CFR Part 46), various guidelines as applicable (both domestic and international, including but not limited to OHRP, FDA, EPA, ICH GCP as specific to IRB review, Canadian Food and Drug Regulations, the Tri-Council Policy Statement 2, and CIOMS), and the ethical principles underlying the involvement of human subjects in research (including the Belmont Report, the Nuremberg Code, and the Declaration of Helsinki).

Advarra has been awarded full accreditation from the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP).

Advarra's IRB is registered with FDA and OHRP.

- IRB Organization (IORG) Number: 0000635
- IRB Registration Number: 00000971
- Advarra's FWA number is 00023875

Please note that the IRB registration number applies for both FDA and OHRP registrations and covers all panels. Advarra's federalwide assurance (FWA) has been approved by OHRP.

1.7. ICH-GCP Compliance

The ICH-GCP Guidelines are voluntary for research conducted in the US. Advarra does not require inclusion of the additional ICH-GCP ICF elements for US research. Additional elements of consent include alternatives and their important risks and benefits. For US studies, Advarra only enforces ICH-GCP compliance in the study ICF when the client submits the ICF with ICH-GCP elements included. When the IRB receives a new US protocol submission that includes a statement regarding ICH-GCP compliance, but the ICF does not include the additional elements, the IRB will not modify the ICF to include those elements.

ICH-GCP Guidelines must be followed for research conducted in Canada. Advarra will ensure inclusion of ICH-GCP elements in the ICF for Canadian research. Advarra expects that Canadian investigators will conduct research in compliance with ICH-GCP, including investigator responsibilities as outlined in Good Clinical Practice (GCP) ICH-E6, Section 4: Investigator.

1.8. Timelines and Advarra IRB Meeting Schedule

The IRB meets at least 12 times per week at regularly scheduled times. In addition, Advarra has Canadian panels that meet 3 times a week. The IRB's meeting calendar is available in CIRBI under Reference Materials. IRB meetings may be scheduled on an ad hoc basis or increased or decreased as appropriate.

Ad hoc meetings are scheduled on an as-needed basis; if faced with critical timelines, please contact Advarra to discuss potential options to meet required timelines.

2. Sponsor and Investigator Responsibilities (U.S.)

2.1. Sponsor Responsibilities

2.1.1. Site Selection/Monitoring

Sponsors are responsible for selecting only investigators qualified by training and experience to conduct a research study.

Sponsors must evaluate and ensure that the appropriate resources and infrastructure to support the conduct of clinical research is maintained at the site(s). The site(s) must be in compliance with the sponsor's requirements for handling medical emergencies.

Sponsors are also required to ensure proper monitoring of the research study and for communicating any finding(s) that may impact subject safety to the IRB. The sponsor must promptly notify the IRB of any decision to terminate an investigator's participation in a research study that was due to noncompliance with the protocol, regulations, or the IRB's requirements or any issue that impacted subject safety.

Please refer to 2.2 Investigator Responsibilities regarding the IRB's expectation of what should be included in a contract (or other funding agreement) with an investigator/site as it relates to subject safety. When the sponsor is working directly with the IRB, the contract should include the responsible party (sponsor or investigator) for submitting this information to the IRB.

2.1.2. Investigational Test Article(s)

The sponsor must ensure that the manufacture and formulation of the investigational product, as well as any comparator (if appropriate) conforms to federal regulations. The sponsor must also ensure the appropriate control (storage, dispensation and accountability) of the investigational product at the site(s) as required by federal, state and local law.

2.2. Investigator Responsibilities

The investigator is responsible for personally conducting, delegating and/ or supervising the conduct of the research and for protecting the rights, safety, and welfare of subjects enrolled in the research. Therefore, prior to agreeing to participate in a study, the investigator should carefully consider the protocol and sponsor requirements.

All investigators should thoroughly review and judge the research design to be sound enough to meet the study's objectives before agreeing to participate in the study. Investigators should thoroughly review the ICF to ensure the adequacy of the information disclosed to subjects, paying careful attention to the risks of the research.

Investigators must ensure that all human subjects research is ethically conducted and in accordance with all applicable federal (including HIPAA if applicable), state/provincial, and local laws and regulations, the IRB's requirements/determinations, and Good Clinical Practice (GCP), as appropriate.

Investigators are responsible for negotiating contracts (or other funding agreements), as applicable, with the sponsor that are designed to contribute to protecting human research subjects participating in sponsored research. The contract should include the following:

- Who is responsible for providing care and who is responsible to pay for it when a subject has a research-related injury. The terms specified in the contract must be consistent with the information provided in the ICF.
- A well-defined time frame for the sponsor to provide routine and urgent data and safety monitoring reports. Investigators are subsequently responsible for reporting these to the IRB.
- That the sponsor will promptly report any findings discovered during a monitoring visit(s), either remotely or in person, that may impact subject safety or influence the conduct of the study. Investigators must report these finding to the IRB for review. The findings reported to the IRB should not include any subject's protected health information (PHI).
- That any findings/new results from a research study discovered by the sponsor, including after the study has ended, that could affect the safety of participants, affect their willingness to continue participation, or influence the conduct of the study will be promptly communicated to the investigator. Investigators must subsequently report this information to the IRB.

Note: *The IRB expects all investigators participating in research and the sponsors of the research to be familiar with both the spirit and intent of the various ethical guidelines, including The Belmont Report, The Nuremberg Code, and the Declaration of Helsinki, as well as applicable local and federal regulations governing human subjects' research.*

Investigators and sponsors are encouraged to review the ethical guidelines, federal regulations, and various guidance documents available in order to become familiar with the ethical principles as well as compliance responsibilities underlying the involvement of human subjects in research. Please contact the IRB with any questions.

Investigators should understand their obligations under GCP as they relate to the following portions of Good Clinical Practice (GCP) ICH-E6, Section 4: Investigator*:*

- *4.1 Investigator's Qualifications and Agreements*
- *4.2 Adequate Resources*

- *4.3 Medical Care of Trial Subjects*
- *4.4 Communication with the IRB/IEC*
- *4.5 Compliance with Protocol*
- *4.6 Investigational Products*
- *4.7 Randomization Procedures and Unblinding*
- *4.8 Informed Consent of Trial Subjects*
- *4.9 Records and Reports*
- *4.10 Progress Reports*
- *4.11 Safety Reporting*
- *4.12 Premature Terminations/Suspension of Trial*
- *4.13 Final Report(s)*

For more information on supervising the conduct of a clinical investigation, see:

- FDA Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects (October 2009)
- OHRP Investigator Responsibilities – FAQs

2.3. Institutional Relationships with the IRB

Many organizations and institutions, including hospitals, academic medical centers, healthcare/hospital systems, and universities, have contractual relationships with Advarra and have designated Advarra as the IRB of record for some or all of their research studies.

Investigators affiliated with such institutions are responsible for complying with the local policies and bylaws of the institution, including obtaining appropriate departmental approvals, fulfilling training and education requirements, and maintaining open communication regarding protocol requirements within applicable departments. Institution-specific requirements should be communicated to the IRB. Investigators/study staff should consult with their local human research protections programs (HRPP) office, applicable research office, or institutional official to determine if there are any additional communication procedures or institutional-specific requirements that must be followed and to determine which studies are eligible for review by Advarra.

Investigators/research staff must ensure that all institutional requirements and approvals have been obtained prior to commencing any human subjects research that has been approved by Advarra.

2.4. Investigator Medical Licensure

The IRB ensures that investigators possess an active medical license, when appropriate, prior to protocol initiation. The investigator's license number (if applicable) is required at the time of initial IRB submission. At the time of initial IRB review, Advarra staff will access the applicable state's licensing board to verify/confirm the investigator's medical license is current and no professional, disciplinary, and/or legal actions exist.

The IRB requires immediate reporting of any change to the investigator's licensure, including any professional, disciplinary, or legal actions.

Please note Advarra is not responsible for monitoring the expiration date of an investigator's medical license.

2.5. Investigator Training

Investigators are expected to have completed training in the conduct of human subjects research. Such training can include topics such as Good Clinical Practice (GCP), federal regulations, and investigator responsibilities. Investigators will be asked to declare their research training during the initial IRB submission process. IRB members will consider the investigator's credentials and training to determine if the investigator is appropriately qualified to conduct the research.

All investigators and their research staff are expected to maintain the qualifications necessary to conduct and oversee the research through ongoing training and experience, including familiarity with the appropriate use of the investigational product(s) as described in the protocol, in the investigator's brochure, in the product information, and in other information sources provided by the sponsor, as applicable.

2.6. Investigator Delegation of Authority

The IRB understands that the investigator may delegate authority for specific activities during the conduct of research studies, i.e. to sub-investigators and/or research coordinators/nurses. If there are study-related activities that are conducted by an individual other than the investigator, the investigator is responsible for the following:

- Ensuring that there is an adequately trained and qualified research team (i.e., sub-investigators). The IRB will not routinely require submission of information relating to sub-investigators/research staff, unless specifically requested by the IRB. When information related to the qualifications of the research team is submitted, the IRB may review this information.
- Delegating research-related tasks to knowledgeable and qualified study staff.
- Ensuring that the research does not commence until the IRB has granted final approval.
- Ensuring that the research is conducted in compliance with applicable federal and local regulations, Good Clinical Practices (GCP), and requirements set forth in the protocol and throughout this document.
- Ensuring that subject complaints, questions, and concerns are adequately addressed in a timely manner.
- Ensuring that the research does not commence until the IND or IDE is in effect. When the research study is submitted prior to or in conjunction with the FDA IND application, subjects may not be consented or screened until after the end of the 30-day FDA review period or after receiving notification from FDA, as consent would be required before study-specific screening activities begin. However, some initial activities related to determining a potential subject's interest in the upcoming study may occur. Such activities should be limited to recruitment efforts to inform potential subjects a study may soon begin on a given condition. However, screening subjects to determine eligibility would not be acceptable until the IND is in effect. For more information, see section 4.5 FDA-Regulated Research.
- For Canadian research, ensuring that the research does not commence until any applicable Health Canada requirements are met (e.g., receipt of Health Canada No Objection Letter for research requiring a Clinical Trial Application).

The IRB expects that the investigator will maintain a list of qualified individuals to whom significant study-related duties have been delegated. Even though specific responsibilities may be delegated, the IRB expects the investigator to personally supervise the conduct of the research, including submissions to the IRB. The investigator maintains responsibility for the protection of the rights, safety, and welfare of subjects under his or her care during the research study.

2.7. Conflict of Interest

An investigator conflict of interest (COI) refers to any interest that competes with the investigator's obligation to protect the rights and welfare of research subjects. One potential source of bias in clinical research is an investigator's financial interest in the outcome of the study due to payment method (e.g., royalty), because the

investigator has a proprietary interest in the product (e.g., patent), and/or an equity interest in the sponsor of the covered research study (for more information, see 21 CFR 54.1[b]).

The IRB requires that a series of questions be answered at the time of initial submission related to financial and non-financial COI relevant to the research protocol. These questions apply to the investigator, the study staff, and their immediate families inclusive of spouse and each dependent child.

Any new financial interests or increased value of a previously reported financial interest that occurs during the course of the study, must be reported to the IRB within 30 business days of the change.

COIs that might adversely affect the protection of subjects must be managed. Investigators must also have procedures in place to manage any actual and/or perceived financial or non-financial COI. Examples of an appropriate management plan may include:

- Require a sub-investigator/research staff member to conduct certain parts of the research, such as the informed consent process.
- Require a sub-investigator/research staff member to collect and report study data.
- Require sub-investigator/research staff member to be involved in recruitment of potential subjects.

If the IRB does not find the management plan acceptable, other protections may be imposed/required.

If the investigator is affiliated with an institution that has an in-house COI committee, the investigator is required to inform the IRB about any determinations, including appropriate management plan, made by the COI committee as it relates to the research being reviewed by the IRB.

Note: *A financial interest related to a research study may be a conflicting financial interest and may affect the rights and welfare of human subjects.*

Refer to HHS's final guidance Financial Relationships and Interests In Research Involving Human Subjects: Guidance For Human Subject Protection *and/or the FDA guidance document* Financial Disclosure by Clinical Investigators.

Other potential sources of bias in clinical research studies include an array of non-financial interests.

2.8. Competing Studies at Research Sites

If a potential subject is eligible for multiple studies conducted at a research site, the investigator should have a procedure in place to address how the investigator and the subject determine which study is most appropriate for the subject.

2.9. Investigational Site(s)

Investigators are expected to maintain the appropriate resources and infrastructure to support the conduct of human subjects research, including protecting the rights and welfare of research subjects and the integrity of the data at their site(s). Investigators should not commence a research study without adequate resources (e.g., personnel, time, and access to a study population) and should discontinue a research study if resources become unavailable.

Investigators are also responsible for being familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current investigator's brochure, in the product information, and in other information sources provided by the sponsor. Investigators must ensure the appropriate control (e.g., storage, dispensation and accountability) of the investigational product as required by federal, state, and local law. Each site must be in compliance with the sponsor's requirement for handling medical emergencies.

If research will be conducted at more than 1 location, the investigator must have a process by which he or she provides oversight for the research at each location, including how often he or she visits each location, how communication occurs between the investigator and research staff, and how often the investigator communicates with the sub-investigators. The IRB must be notified of each of the locations.

For research studies conducted at an international location, the investigator must obtain permission to conduct research in the country by certification or local ethics review, when one exists. It is the IRB's expectation that the investigator will follow local laws, regulations, customs, and practices. Please contact the IRB for additional information on conducting international research.

When following ICH-GCP (E6), investigators/research staff must understand the responsibilities as noted in section 4 of ICH-GCP.

2.10. Investigator Study Records

Investigators are expected to:

- Ensure that research records are stored at each investigative site in such a way as to protect the confidentiality of subject information.
- Maintain accurate and complete study records.
- Make those records available for inspection by the IRB.
- Provide the IRB with any required information before, during, or after the study.

2.11. Physician Notification/Referrals

During and following a subject's participation in a study, the investigator should ensure that adequate medical care is provided to a subject for any adverse events related to the trial, including clinically significant medical laboratory values.

In accordance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) 4.3.3, ICFs may include an option for a subject to instruct the investigator to notify the subject's primary care physician (PCP) or appropriate specialist of the subject's participation in the clinical research study. If a subject opts to have his or her PCP/specialist notified, the investigator must send a letter to the PCP or the appropriate specialist. It is recommended that the letter describe the purpose of the study, the length of the study, the randomization schema, and a brief summary of the study procedures. The letter should also invite the PCP/specialist to contact the investigator with further questions. If a protocol requires PCP notification, the subject is not given the option to decline notification. Advarra does not routinely require PCP notification.

2.12. Relevant Findings

When the investigator is the lead investigator of a multisite study, or the investigator's organization is the lead site of a multisite study, a description of the management of information obtained in the multisite research that might be relevant to the protection of research participants, such as unanticipated problems, interim results, and protocol modifications, must be submitted to the IRB.

2.13. Sponsor Audits

Sponsors and investigators must promptly notify the IRB about any sponsor or CRO audit resulting in the sponsor suspending or terminating the study at the site(s). A summary of the reasons for the suspension (and required corrective action[s]) or termination is also required.

The IRB will review the information and take appropriate action (e.g., suspend enrollment, terminate IRB approval, etc.), including determining if the corrective action plan is appropriate. The IRB will also report any suspension or termination of IRB approval to the appropriate regulatory authority.

2.14. Federal, State, Local, and International Requirements

It is the responsibility of the investigator/research staff and sponsor to be familiar with and comply with federal (including HIPAA if applicable), state, provincial, local laws, codes and guidance governing their research, in addition to the requirements listed in the investigator's agreement.

Investigators are responsible for communicating any applicable state/local research requirements to the IRB at the time of initial submission.

Investigators/research staff are responsible for understanding and complying with their local institution's by-laws, and policies and procedures as they relate to the conduct of research. Investigators/research staff are also required to understand and comply with the IRB's and the institution's agreement related to which studies can be reviewed by the IRB, as well as institutional requirements for submitting to the IRB.

For research studies conducted at an international location, the investigator must obtain permission to conduct research in the country by certification or local ethics review, when one exists. It is the IRB's expectation that the investigator will follow local laws, regulations, customs, and practices. Please contact the IRB for additional information on conducting international research.

3. Working With the IRB

3.1. Submission Process

3.1.1. Electronic Submission via the Advarra Center for IRB Intelligence (CIRBI) Platform

Advarra utilizes a highly customized, cloud-based electronic platform to facilitate research study submissions, regulatory compliance, and e-processing and tracking of research studies. The electronic platform is called the Advarra Center for IRB Intelligence (CIRBI) Platform and allows real-time communication among sponsors, research sites, institutional representatives, and Advarra staff and IRB members. All parts of the IRB process from initial submission to study close-out/termination are supported by CIRBI.

Note: *Please contact the CIRBI Help Desk at 1-866-99CIRBI (1-866-992-4724) or email CIRBI@advarra.com with any questions.*

3.2. Protocol Submission Requirements

Sponsors may submit a research study for review prior to or in conjunction with identification of the investigators/sites. This allows the IRB to review and approve the research study and finalize the master ICF for use by the investigators/sites.

An investigator may also submit a research study directly for review and approval (i.e., single site study). In this scenario, the investigator (or designee) is responsible for submitting all required protocol documentation as well as the information in 3.4 Investigator and Site Submission Requirements.

Information required for IRB review of a research study includes:

- Finalized protocol

- Product information (e.g., investigator brochure, package insert, device instructions for use), if applicable
- Sponsor-approved ICF (Advarra staff will insert the site-specific language into the sponsor-approved ICF, if applicable)
- Subject-facing materials (e.g., recruitment material, diaries, questionnaires, etc.)
- Federal grant, if applicable (not required for studies submitted on or after the Compliance Date; see 4.6.1 Federalwide Assurance [FWA] for more information)
- For multicenter research funded by HHS, the HHS-approved sample consent document and full HHS-approved protocol (when they exist)

The IRB expects that the protocol or protocol-related documents (e.g., protocol clarification/administrative letters or other protocol supporting documentation) include accurate and detailed information about the conduct of the research. When the submission forms include information that conflicts with the information in the protocol, Advarra staff will follow-up with the submitting party.

When the ICF includes information that conflicts with the information in the protocol, the IRB will modify the ICF to align with the protocol. This includes deleting language from the ICF when it is not supported by the protocol. The submitting party may decide to later submit additional revisions to the ICF as a modification.

When the ICF includes additional information that is not included in the protocol, the IRB will determine if the protocol or ICF needs to be revised. Generally, the ICF will be updated to be consistent with the protocol.

Provided that the additional information in the ICF does not conflict with the protocol and is expanding on information subjects may need to make an informed decision (e.g., subject restrictions), revisions to the protocol will generally not be required.

The IRB will rely on the protocol as the main source of authority for the description of the conduct of the research. If there is a discrepancy between the submitted ICF and the submission form, the protocol will be reviewed for verification of the correct information. If the protocol does not address the area that is conflicting, Advarra staff will follow up.

3.3. Data Monitoring

As appropriate, the research plan should make adequate provisions for monitoring the data collected to ensure research subject safety (see note below for more information). For example, studies that are greater than minimal risk must implement a monitoring plan or data monitoring committee (DMC)/data and safety monitoring board (DSMB) to ensure the safety of research subjects. Any research study greater than minimal risk requires an appropriate plan for monitoring the data collected to protect the safety and welfare of the research subjects. Sponsors and investigators should consider the size, complexity, phase, and level of risk involved in the research when determining whether a monitoring plan or formal DMC/DSMB is appropriate. In addition, sponsors and investigators should understand that monitoring might occur at specific points in time, after a specific number of participants have been recruited, or upon recognition of unexpected harms.

A formal DMC/DSMB should be considered for research involving intervention that entails potential serious risk to subjects, compares blinded treatments over a long period of time, or which may call for "stopping rules" for certain endpoints to further protect the safety or welfare of subjects. If a DMC/DSMB has been established and the plan is not clearly delineated in the protocol or submission form, a detailed description of the DMC/DSMB's operation (e.g., membership, function, frequency of review, stopping rules) may be requested.

Any recommendations made by a DMC/DSMB that address the safety of subjects and potentially impact their willingness to continue in the study must be submitted to the IRB. In addition, results from any study that could directly affect subject safety or the subject's medical care must be submitted to the IRB.

While all greater than minimal risk studies must include some form of safety monitoring, not all require monitoring by a formal committee that is external to the investigator and sponsor. The size, complexity, phase, and level of risk involved in the research should be considered when assessing the need for or appropriateness of a monitoring plan or DMC/DSMB. If a DMC/DSMB has been established and the plan is not clearly delineated in the protocol or submission form, a detailed description of the DMC/DSMB's operation (e.g., membership, function, frequency of review, stopping rules) may be requested.

Note: *As part of their obligation to protect subjects, the IRB expects sponsors and investigators understand the concept of minimizing risks. Sponsors and investigators should design research that incorporates a plan to monitor data for the safety of subjects. The IRB considers the following provisions for monitoring data to ensure subject safety during the review of research (as applicable):*

- *The type of safety information that will be collected, including SAEs.*
- *The method for collecting safety information (e.g., study visits, case report forms, etc.).*
- *The frequency of data collection.*
- *The frequency of review of cumulative safety data.*
- *The composition of a data monitoring committee and a plan for reporting the data monitoring committee's findings to the IRB, including the frequency of reporting.*
- *Additional protections for monitoring the data for studies that are blinded, have multiple sites, enroll vulnerable populations, or employ high-risk interventions.*
- *When a data monitoring committee is not used, and if applicable, statistical tests employed for analyzing the safety data to determine whether harm is occurring.*
- *Provisions for the oversight of safety data.*

3.4. Investigator and Site Submission Requirements

Each investigator is required to submit investigator and site information for IRB review. This information must include the details of the informed consent process, plans for subject recruitment, and information about the location(s) where the research is conducted. The following documents are also required during the submission process, as applicable:

- Current curriculum vitae (CV) of the investigator that includes current position/organization and demonstrates appropriate experience and knowledge to conduct the research and/or provide medical supervision of subjects.
- Regulatory agency audits of the site and/or investigator from the last 5 years. The submission should include the response to the regulatory agency audit that addresses the findings (if applicable).
- Additional text for the ICF may be submitted for multisite studies for which Advarra is the central IRB. The investigator and site have the option to request modifications to the IRB-approved ICF to address site specific needs, including compensation for study participation details. **Note:** *Sponsor approval may be required for changes to the master ICF.*
- Standard operating procedures may be included when the responses from the investigator and site submission do not accurately address the processes at the site, including the informed consent process.
- When the investigator is at an institution that has a local IRB, an IRB authorization agreement (IAA), waiver of IRB oversight document, or reliance agreement must be submitted, indicating that the local IRB waives study oversight authority to Advarra. If a global waiver, master service agreement (MSA, or IAA is already in place with Advarra that covers all studies, additional documentation is not required.

- Recruitment material, including any advertising for study subjects, is considered to be the start of the informed consent process. Recruitment material and any changes to the content or presentation of approved recruitment material must be reviewed and approved by the IRB prior to use.
- For Canadian Federally-funded research subject to the TCPS2 only, a copy of the clinical trial budget.

Note: *With Advarra's IRB-Ready® service, available through CIRBI, a significant amount of investigator information will automatically populate on all subsequent submissions after the first time an investigator applies for initial review and approval. This reduces administrative burden and decreases site approval timelines.*

3.5. Informed Consent Form (ICF) and Assent

The ICF must be submitted in a Microsoft Word-compatible format.

Research studies which include subjects who are minors generally require the submission of an assent statement and/or an assent form for IRB review. The IRB requires the use of an assent statement (which is a separate signature block) for subjects who are minors but who are old enough to understand the ICF as written (approximately age 14 through 17). An assent form is required when subjects (typically between the ages of 7 and 13) need information presented to them in age-appropriate language. For most studies, subjects 6 years old or younger are not required to sign an assent statement or assent form.

The IRB may determine assent is not necessary if the capability of some or all of the children is so limited that they cannot reasonably be consulted, or 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 study.

3.6. Transfer Studies or Studies Disapproved by Another IRB

Advarra will review requests for transferring IRB oversight from another IRB. The transfer of oversight responsibility for a research study from one IRB to another should be accomplished in a way that assures continuous IRB oversight with no lapse in either IRB approval or the protection of human subjects, and with minimal disruption of research activities.

Based on the nature of the request for transfer and the condition of the previous IRB review and oversight, the IRB will determine which of the following forms of review is appropriate:

- Undertake an initial review, either by the convened IRB or under an expedited review procedure.
- Undertake a continuing review at the time of transfer, either by the convened IRB or under an expedited review procedure.
- Not undertake a review until the next continuing review date.

The start of the Advarra approval period marks the effective date for the transfer of IRB oversight. This date will be documented on correspondence to the investigator and original IRB. Following the effective transfer of IRB oversight to Advarra, the requestor of the transfer is responsible for taking the actions necessary to close IRB oversight with the original IRB.

If the study was disapproved by another IRB, the submission to Advarra must include the reasons for the disapproval.

3.7. Submission of 1572s

Advarra does not require 1572s be submitted at initial review or when revisions to the 1572 are made.

4. IRB Review

4.1. IRB Review Process

Upon receipt, Advarra staff members perform an administrative review and obtain any clarifications necessary for IRB review. The protocol is then sent for either non-human subjects research or exempt determination, or expedited or full board review, as appropriate.

The possible outcomes of the IRB review include:

- **Non-human subjects research**
- **Exempt**
- **Approved**—The proposed research or research activity is approved as submitted
- **Approved with modification**—The proposed research is approved with the restrictions and/or changes required by the IRB
- **Deferral**—The proposed research does not include enough information to determine if the IRB approval criteria are met
- **Disapproval**—The proposed research does not meet the IRB approval criteria and cannot be conducted

Note: *To determine if a project qualifies as "engaged in human subjects research" (and therefore needs an FWA), refer to* OHRP's Guidance on Engagement of Institutions in Human Subjects Research.

The IRB may take an action to approve or approve with modification(s) a research study submitted for review. Once a research study is approved with modification(s), it is considered approved and can be conducted in accordance with the changes referenced in the approval with modifications letter and any revised documentation issued with the approval documentation. The IRB-instituted modifications are either delineated in the letter, included in tracked changes documentation, or both. Once an approval with modifications letter has been issued, no further response is required unless the IRB specifically requests the submission of protocol documentation, or the instituted modifications are being appealed by the submitting party.

The IRB may require revisions to the protocol to meet the criteria used to approve research. When the responses change the conduct of the research, the following methods of response are considered acceptable:

- Revised protocol
- Protocol amendment
- Protocol clarification letter
- Administrative letter
- Protocol addendum
- Letter from the sponsor/CRO on letterhead

If the responses do not change the conduct of the research, responses may be accepted via an email submitted through CIRBI (e.g., responses to IRB questions regarding the rationale or background for a study design, confirmation of IRB interpretation).

The IRB may defer taking an action when there is additional information or revised protocol documentation needed. Once the required information is received by the IRB, the proposed research study is scheduled for re-review by the IRB panel that last reviewed the submission.

If the protocol has been disapproved, a disapproval letter is sent to the submitting party via CIRBI outlining the reason(s) for disapproval and an appeal process. The appeal process includes the following options:

- Resubmit the project with the modification(s) that address the IRB's findings and criticism(s); or
- Provide a written justification for relief of any IRB imposed condition or disapproval.

The IRB then decides whether to reconsider the research study during a convened meeting and notifies the appropriate parties of its final determination.

Note: *IRB-imposed modifications to the research may also be appealed if the sponsor/investigator provides a rationale/justification as to why the modification is not appropriate.*

4.2. IRB Suggestions

The IRB may make suggestions regarding the protocol and consent documents when the recommended changes are **not** necessary in order to meet regulatory requirements but may assist the client in more thoroughly describing information located in the study documents or that may be considered for future studies. The IRB will clearly state whether a change is a suggestion or requirement.

4.3. Expedited Review

Federal regulations allow for some research activities to be reviewed via expedited review procedures. Advarra staff and IRB members follow the federal regulations for expedited review (21 CFR 56.110 and 45 CFR 46.110) and the Categories of Research That May Be Reviewed by the IRB via Expedited Review (Federal Register), as applicable. If submitted research is not approvable under expedited review, it is brought before the IRB during a convened meeting.

Note: *The IRB always makes the final determination as to whether submitted research qualifies for expedited review. In cases where research appears to qualify for expedited review but the IRB reviewer subsequently determines that the research must go to full board, full board timelines will apply.*

4.4. Exempt Research

Some federally funded and FDA-regulated research may be exempt from IRB review and oversight (45 CFR 46.101(b); 21 CFR 56.104: TCPS2 2.2-2.4). In determining whether the proposed research meets the criteria for exemption, the IRB also determines whether or not the proposed research is ethically sound and that adequate provisions are made for the protection of the research subjects, including:

- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of data.
- If there are interactions with subjects, appropriate information about the research activity is disclosed to subjects prior to enrollment.
- There are adequate provisions to maintain the privacy interest of subjects.
- Subjects are equitably selected to participate in the research.

For certain categories of exempt research submitted on or after the Compliance Date, there is a requirement for limited IRB review to ensure that conditions specified in the Revised Common Rule are met, including adequate provisions to protect privacy of subjects and confidentiality of data. This review will be conducted by the IRB at the same time as the review to determine whether the proposed research meets the criteria for exemption.

If the IRB determines that a research protocol is exempt from the applicable regulations, this determination is communicated to the submitting party via a determination letter in CIRBI. The letter includes instructions to submit any future modifications to the research to the IRB to ensure that the activities continue to qualify as exempt.

The IRB expects exempt research will be conducted following the ethical principles outlined in the Belmont Report, the Nuremberg Code, and the Declaration of Helsinki, and that investigators will ensure that subjects are appropriately protected during the research.

Research determined to be exempt from IRB oversight does not require continuing review.

4.5. FDA-Regulated Research

A sponsor is responsible for determining whether an investigational new drug (IND) or investigational device exemption (IDE) application is required for the proposed research. The IRB requires that the IND/IDE number be submitted at the time of initial review. If the sponsor indicates that an IND is not required, the IRB may request additional supporting documentation (e.g., letter from the sponsor or FDA, other basis for that determination) be provided for review. If the IRB is questioning whether an IND or IDE is required and is unable to resolve this issue, the IRB may delay approving the study pending additional information/documentation from the FDA.

For studies that require an IND or IDE application, it is the IRB's expectation that study activities, including advertising, recruitment, and screening, will not begin until after the end of the 30-day FDA review period or after receiving notification from FDA.

Many Phase I units request to begin study recruitment prior to the 30-day FDA review period. While some initial activities related to determining a potential subject's interest in the upcoming study may occur, such activities should be limited to recruitment efforts to **inform** potential subjects a study may soon begin on a given condition. However, screening subjects to determine eligibility would not be acceptable until the IND is in effect.

Any FDA-required changes based on the IND or IDE submission should be submitted to the IRB for review and approval prior to implementation.

4.6. Health Canada-Regulated Research

A sponsor is responsible for determining whether a Clinical Trial Application or Investigational Testing Authorization (ITA) application is required for the proposed research. The IRB does not require submission of Health Canada No Objection Letters (NOL), Notices of Authorization (NOA) or Investigational Testing Authorization Letters. If the sponsor indicates that a CTA/ITA is not required, the IRB may request additional supporting documentation (e.g., letter from the sponsor or Health Canada, other basis for that determination) be provided for review. If the IRB is questioning whether CTA or ITA is required and is unable to resolve this issue, the IRB may delay approving the study pending additional information/documentation from Health Canada.

For studies that require a CTA or ITA, it is the IRB's expectation that study activities, including advertising, recruitment, and screening, will not begin until after receiving notification from Health Canada or until the end of the applicable Health Canada review period.

Any Health Canada-required changes based on the CTA or ITA submission should be submitted to the IRB for review and approval prior to implementation.

4.7. Federally Funded Research

4.7.1. Federalwide Assurance (FWA)

Every institution engaged in non-exempt human subjects research supported or conducted by the Department of Health and Human Services (HHS) must obtain an assurance of compliance approved by the Office for Human

Research Protections (OHRP). The assurance formalizes the institution's commitment to comply with the requirements set forth in the regulations for the protection of human subjects at 45 CFR Part 46.

The arrangement between the FWA-holding institution and Advarra must be documented in writing. Advarra can provide a study-specific or global IRB authorization agreement (IAA), reliance agreement, or master service agreement (MSA) that must be signed by both parties.

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Protocol submissions funded by the Department of Defense (DoD) are subject to additional regulatory requirements under 32 CFR 219 and Instruction 3216.02 and thus require additional consideration by the IRB as noted below.

Institutions conducting the DoD-supported research for which Advarra serves as the IRB of record are responsible for:

- Providing the IRB with documentation of any scientific review at the time the IRB application is submitted.
- Implementing an initial and continuing education/training policy for human subjects research and determining that the investigator and research team have met internal requirements.
- Ensuring review by the human research protection official (HRPO) following IRB review.
- Promptly reporting to the DoD HRPO significant changes to the research protocol approved by the IRB, results of continuing review, determinations of serious or continuing noncompliance, incidences/events determined to be unanticipated problems, and any other DoD reporting requirements. This reporting should occur within 30 days or sooner as negotiated between DoD and the institution.
- For international research, ensuring the investigator has permission to conduct research in that country by certification or local ethics review, when one exists.
- Ensuring the investigator follows all local laws, regulations, customs, and practices.

4.7.2. National Institute of Health (NIH) Funded Research

All biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by the NIH Intramural Research Program, that collects or uses identifiable, sensitive information will be issued an automatic Certificate of Confidentiality (CoC) by NIH as part of the award itself. A CoC protects an investigator from certain disclosures of private information about participants. Whether a CoC has been issued is relevant to the IRB's assessment of the adequacy of the measures in place to protect the privacy of subjects and to maintain the confidentiality of data. Regulations require that the ICF include a description of confidentiality. Additionally, NIH has stated that it is expected that the investigator will inform participants about the CoC.

When a CoC has been issued for a study, it should be described in the ICF. Advarra will add descriptions of CoCs to ICFs for all NIH-funded studies when these are submitted without the CoC noted in the ICF.

4.8. Research Regulated by the Environmental Protection Agency (EPA)

In addition to the basic procedures and protections contained in the EPA enactment of the Common Rule, 40 CFR 26, the EPA Final Rule Protection for Subjects in Human Research Involving Pesticides (April 2013) also requires investigators who propose to conduct new research covered by the rule to submit protocols and other materials for science and ethics review by both EPA and/or the Human Studies Review Board (HSRB). The HSRB is a federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App.2 § 9. The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of

human subjects research. The HSRB review of proposed new research would occur following its review and "approval by the IRB," and after EPA has completed its review.

It is the investigator's responsibility to ensure that required subsequent reviews by EPA, by the Human Studies Review Board (HSRB), and (if the research is to be conducted in California) by the California Department of Pesticide Regulation (CDPR) have been completed before initiation of the study.

The IRB requires submission for review and approval recommendations by EPA, HSRB, or CDPR incorporated into revised proposals before enrollment of any research subjects in the study.

Initiation of a study conducted for submission to EPA before obtaining all required regulatory reviews (including when applicable subsequent EPA or HSRB review) or before final approval of the protocol, ICFs, and supporting materials by the reviewing IRB is a violation of EPA regulations and will be considered noncompliance.

In 2006, the EPA amended its regulation at 40 CFR part 26 to include additional protections for vulnerable subjects within its subparts. Subpart B of the regulation is a ban on intentional exposure research involving pregnant women, nursing women, and children. Research involving intentional exposure of a human subject is defined in 40 CFR part 26.202 as the "…study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study."

Subparts C and D of 40 CFR Part 26 seek to ensure that vulnerable subjects are protected in observational research. Subpart C provides additional protections for observational research conducted with pregnant women as participants. Subpart D adds protections for observational research conducted or supported by EPA involving children as participants. Observational research is defined in 40 CFR part 26.302 as any human research that does not meet the definition of research involving intentional exposure of a human subject.

The distinction between intentional exposure research and observational research is extremely important for EPA investigators in the development and approval process for studies involving human subjects. Since intentional exposure research involving pregnant women, nursing women, and children is banned, investigators must pay close attention to the details of their study in order to ensure that it does not meet the definition of intentional exposure if the study involves these protected populations.

EPA also added special regulations at 40 CFR part 26, subparts K-L, which are related to the review of third-party pesticide research involving human participants. These regulations were updated in 2013. The 2013 Final Rule amended 40 CFR 26 to disallow consent by a legally authorized representative in third-party studies because the types of research that are conducted on pesticides should not use subjects who cannot consent on their own behalf.

See EPA's website for further information.

4.9. Unplanned Emergency Use of a Test Article

The FDA regulations define "emergency use" as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval. In the event of the emergency use of a test article when there is no time to obtain IRB approval, please follow the FDA regulations found in 21 CFR 56.104(c). The use should be reported to the IRB within 5 working days. Please consult Advarra staff for additional instructions and guidance regarding any subsequent use of the test article.

In the event that an unexpected life-threatening emergency requires the use of a test article when informed consent cannot be obtained, please follow the FDA regulations found in 21 CFR 50.23. Both the investigator and an independent physician should certify in writing all of the following:

- The human subject is confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent cannot be obtained from the subject.
- There is insufficient time to obtain consent from a legally authorized representative.
- No alternative method is available that provides an equal or greater likelihood of saving the life of the subject.

If time is not sufficient beforehand, please obtain the determination of an independent physician after the fact.

Under FDA regulations, the emergency use of a test article other than a medical device is a clinical investigation; the patient is a research subject, and the FDA may require data from an emergency use be reported in a marketing application.

If the investigator's organization follows HHS requirements (under the institution's FWA), or if the research study is also subject to HHS regulations due to federal funding, patients receiving emergency use of a test article as defined by FDA regulations may not be considered to be a research subject. HHS regulations do not permit the use of data obtained from patients to be classified as human subjects research, nor do they permit the outcome of such care to be included in any report of a research activity subject to HHS regulations.

Please note that any anticipated subsequent use of the test article is subject to IRB review and approval.

4.10. Expanded Access

Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials. The terms "compassionate use," "treatment IND" or "treatment protocol," and "preapproval access" are also occasionally used in the context of using an investigational drug to treat a patient.

The main distinction between the use of an investigational drug in the usual studies covered under an IND and expanded access is that expanded access uses are not primarily intended to obtain information about the safety or effectiveness of a drug.

Under FDA's current regulations, there are 3 categories of expanded access:

- Expanded access for individual patients, including for emergency use (21 CFR 312.310)
- Expanded access for intermediate-size patient populations
    - Generally smaller than those typical of a treatment IND or treatment protocol — a treatment protocol is submitted as a protocol to an existing IND by the sponsor of the existing IND (21 CFR 312.315)
- Expanded access for widespread treatment use through a treatment IND or treatment protocol
    - Designed for use in larger patient populations (21 CFR 312.320)

In the case of emergency expanded access use, FDA authorization is still required (21 CFR 312.310[d]), but it is not necessary to wait for IRB approval to begin treatment. However, the IRB must be notified of the emergency expanded access use within 5 working days of emergency use (21 CFR 56.104[c]). Generally, once an investigational drug is used in an emergency situation without prior IRB approval, any subsequent uses of the investigational drug at that same institution would require prior IRB review and approval (21 CFR 56.104[c]). An institution or physician that expects subsequent use of the investigational drug should request review and approval by the appropriate IRB after the initial emergency use.

If a physician submitting an individual patient expanded access IND to the FDA indicates a request to waive full IRB review requirements under 21 CFR 56.105, and FDA concludes that such a waiver is appropriate for individual patient expanded access INDs, then the submission may be reviewed by the IRB chairperson or another designated

IRB member instead of the convened IRB. This provision does not apply to other types of expanded access requests, including requests for expanded access for medical devices.

Expanded access to an investigational drug for treatment use, including emergency use, requires informed consent as described in 21 CFR part 50, unless one of the exceptions found in part 50 applies.

Expanded access submissions are subject to continuing review requirements.

5. Subject Recruitment

The IRB requires prospective review of all recruitment materials that are intended to be seen or heard by prospective subjects to solicit their participation in a research study.

Investigators are responsible for understanding the importance of equitably recruiting and selecting research subjects (subject selection should be representative of the group that will benefit from the research), as well as implementing appropriate recruitment techniques.

5.1. Recruitment Materials

Recruitment material must be consistent with the IRB-approved protocol and ICF. In addition to following the requirements outlined in this document, the IRB requires that recruitment material follow the FDA Information Sheet on Recruiting Study Subjects.

Recruitment material and any modifications made to the content or presentation of approved recruitment material must be approved by the IRB prior to its use. While the IRB reviews scripts for audio and video recruitment materials, the final audio and/or video version must also be submitted to the IRB for review.

Examples of the types of recruitment material requiring IRB review include:

- Newspaper advertisements
- Radio advertisements
- Posters
- Television advertisements
- Internet advertisements
- Telephone screen scripts
- Recruitment letters
- Flyers
- Bulletin boards or billboards

Please note that clinical trial listings, such as those seen on clinicaltrials.gov, are not considered to be recruitment materials by the IRB.

Recruitment material should be limited to the information a prospective subject needs to determine their eligibility and interest in the research, such as:

- The name and address of the investigator and/or research site.
- The condition under study and/or the purpose of the research.
- The criteria that is used to determine a subject's eligibility for the study in summary.
- A brief list of study participation benefits, if any, and the risks for participating in a research study.
    - A description of any benefits of the study must be balanced with the risks of the study.

- The amount of time or other commitment required of the subjects in the study.
- The location of the research site and the name of the person or office a potential subject can call to obtain additional information.

The IRB requires that recruitment material must:

- Be clear that information concerns a research study.
- Be clear about what is investigational.
- Be clear in the procedures that are "study-related."

The IRB requires that recruitment material must **not**:

- Be unduly coercive or promise/imply a certainty of cure, favorable outcome, or other benefit beyond what is contained in the IRB-approved protocol and ICF.
- Make any claim, explicitly or implicitly, that the test article is safe or effective for the purpose being studied, or that the test article is equivalent or superior to any other test article (drug, biologic, or device).
- Use the word "new" without being clear as to what is the test article.
- Promise "free medical treatment" when the intent is only to say that subjects are not charged for participating in the study.
- Use exculpatory language.

Recruitment material may state that subjects are paid, if applicable, but should not emphasize the payment or the amount to be paid by such means as larger or bold type. When referring to subject compensation in recruitment material, it is recommended that it be balanced by a description of subject responsibilities during the study (for example, how many study visits is part of participation).

Print advertisements must be submitted in final format (free of typographical, grammatical, and spelling errors) and include any graphics that are used.

Radio and television scripts should be reviewed and approved prior to taping to avoid re-taping, if modifications are required. Radio scripts being utilized for live broadcast use must be read exactly as approved by the IRB. Audio/visual recruitment materials should be submitted in final format after written script approval is received.

Press releases require IRB review if they mention a specific study and will be seen by potential subjects. They are then considered recruitment material and their content would be guided by the same regulations as other recruitment.

- **Studies conducted under the Old Common Rule:** Screening tools (such as telephone screening scripts, online questionnaires, etc.) that collect personal private information from potential subjects must contain the IRB-required elements of consent. The IRB can waive the requirement for documentation of consent for these screening tools.
- **Studies conducted under the Revised Common Rule or FDA regulations only**: Information or biospecimens for screening, recruiting, or determining subject eligibility may be obtained without the informed consent of the subjects if (1) information is obtained through oral or written communication with the subject, or (2) identifiable information or identifiable biospecimens are obtained by accessing records or stored specimens. If screening tools are used (such as telephone screening scripts, online questionnaires, etc.), these still require review by the IRB.

5.2. Recruitment Material Translations

Advarra uses a third-party vendor to translate recruitment materials for the sponsor and/or the site. Once the materials are translated, Advarra provides the translated document(s) and the affidavit of accuracy/translation certificate to the client. If the sponsor chooses to translate the materials, the translated document(s) and the affidavit of accuracy/translation certificate should be submitted to the IRB for acknowledgement.

Note: *If a sponsor has a quality control (QC) process that includes reviewing and making potential administrative edits to final translated documents (e.g., a certificate of translation has been issued), the translated document(s) will be sent back to the vendor for confirmation that the QC edits are consistent with the IRB-approved English version, and a new certificate will be required/issued.*

5.3. Finder's Fees and Referral Incentives

The IRB does not approve of "finder's fees" or payments made to the investigator or research staff, as these incentives/bonuses may be considered to be unethical and unduly influencing. Incentives/bonuses paid to research staff for recruitment and retention may represent a potential conflict of interest for both staff and the site; payment should only be made for specific study-related work performed by the site as outlined in the research protocol.

The IRB will consider proposals to provide payment or other incentives to referring physicians on a case by case basis. The IRB will generally not approve proposals to provide payment based on the number of participants identified, referred, or enrolled. Such incentives are considered unethical and raise concerns regarding undue influence. However, the IRB may approve proposals to pay referring physicians a reasonable amount for, e.g., their time spent reviewing medical records to determine study eligibility.

In addition, the IRB does not approve of "finder's fees" or payments to subjects in exchange for referrals of potential subjects unless they are judged not to increase the possibility of coercion or undue influence on subjects by using unreasonable compensation or unreasonable conditions for distribution of compensation. If such a program is being considered, notification and a description of the program must be submitted to the IRB prior to implementation. The IRB will then assess whether the program directly impacts the subjects' rights or welfare.

6. Informed Consent

6.1. Informed Consent Process

Informed consent is an ongoing, continuous process that encompasses presenting any ICF clearly and carefully as well as assessing subject consent through the study. Presenting the ICF clearly and carefully includes giving the subject ample opportunity to ask questions and the ability to take the ICF home to review, as necessary and appropriate. A copy of any ICF should always be given to subjects after they have signed and dated the document.

Investigators are responsible for delegating the process of obtaining informed consent to properly trained research staff, as appropriate. Research staff obtaining informed consent must understand the research, be able to answer questions the potential subject might have and be experienced in conducting the informed consent process.

Investigators and research staff should assess subject consent throughout the study and be responsive to subjects' complaints, concerns, and/or questions.

To comply with conditions of IRB approval, the following procedures must be followed:

- The investigator does not involve an individual in the research study unless the investigator or designated staff has obtained the legally effective informed consent of the subject (or of the legally authorized representative [LAR] if approved by the IRB).
- Subjects are provided sufficient opportunity to consider whether or not to participate in the research.
- The consent process minimizes the possibility of coercion or undue influence.
- The consent discussion is in a language understandable to the subject or LAR.
- The consent discussion is free of any exculpatory language.
- The most recent IRB-approved version of the ICF is used.
- The subject is given adequate time and place to read and review the ICF.
- The subject is given the opportunity to take the ICF home for review prior to signing the document, as appropriate.
- Any consent discussion provides ample opportunity for the investigator or designated research staff to be available to answer any questions the subject or LAR may have.
- Each person on the IRB-approved ICF signs and dates the document on the same visit, as appropriate.
- The subject receives a signed and dated copy of any ICF.
- **Studies conducted under the Old Common Rule:** Consent must be obtained before conducting research-only procedures (including the collection of personal, private information).
- **Studies conducted under the Revised Common Rule or FDA regulations only**: Personal private information may be obtained without consent if it is obtained through oral or written communication with the subject, and identifiable information and identifiable biospecimens may be obtained without consent by accessing records or stored specimens.

6.2. Re-Consent

When there are significant changes in a research study, the IRB may require that all active subjects be re-consented. These subjects should be presented with a revised ICF that includes the new study information and should sign the revised ICF if they wish to continue to participate in the research.

Re-consenting by mail is allowable in appropriate circumstances. This is something that needs to be assessed by the investigator and documented by the site. Re-consenting by mail can be managed by mailing 2 new ICFs to the subject and asking him or her to call the investigator to discuss the changes. After discussion, he or she should sign and return the signed ICF to the study site.

In some cases, there is new meaningful information that becomes available in a study, and the IRB may require the investigator to provide an information sheet to subjects but not require re-consent.

6.3. Subject Withdrawal from a Research Study

After providing consent, a subject may decide to prematurely terminate his or her participation in a research study. Although a subject is not obliged to give his or her reasons for withdrawing prematurely from a research study, the investigator should make a reasonable effort to ascertain the reason while fully respecting the subject's rights.

According to FDA, when a subject withdraws from a research study, the data collected on that subject up to the point of withdrawal remains part of the study database and may not be removed. If a subject withdraws from a study, removal of data that were already collected may undermine the scientific as well as the ethical integrity of the research. The ICF cannot give the subject the option of having data removed.

The protocol and ICF should state that the participant may withdraw at any time. The protocol does not need to describe the specific process to withdraw from the research, but this more detailed information does need to be included in the ICF. The protocol does not need to have all the details relating to the withdrawal process (e.g.,

specifically stating the subject may request at any time that all samples be destroyed or that the request to withdraw needs to be in writing). This level of detail can be in the ICF and **not** the protocol.

When a subject wishes to withdraw participation in a research study, the IRB recommends that the investigator explain to the subject the importance of obtaining follow-up safety data about the subject, especially in clinical trials evaluating safety and effectiveness of an intervention. Subsequently, the investigator may ask the subject to clarify whether he or she 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 that the subject initially consented to may continue, such as: (1) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging), or (2) obtaining identifiable private information from the subject's medical or educational records or from the subject's healthcare provider(s).

If a subject withdraws from the interventional portion of the study but agrees to continued follow-up of associated clinical outcome information, 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 ICF). IRB approval of such ICF(s) would be required.

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 the subject's medical record or other confidential records requiring the subject's consent for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study and may also consult public records, such as those establishing survival status.

7. Informed Consent Forms (ICFs)

The IRB reviews the submitted ICF(s) to ensure that the information is accurate, complete, and that all elements of consent outlined in the applicable regulations are present.

The investigator, together with the sponsor and the IRB, is responsible for review of the IRB-approved ICF to ensure that the information conveyed to the subject is accurate. The investigator may request site-specific changes to the IRB-approved ICF by submitting a modification request in CIRBI.

7.1. Health Insurance Portability and Accountability Act (HIPAA)

Advarra will review HIPAA authorization language when it is included in or appended to the ICF. If HIPAA authorization language is not included in or appended to the ICF, it is the investigator's/site's responsibility to comply with all HIPAA requirements.

7.2. Use of the Short Form Consent

When investigators reasonably expect that the subject population for a proposed study will include individuals who do not understand English and can anticipate the specific language(s) that they will understand, the investigator should request a translation of the IRB-approved study ICF (or "long form") and any study documents that will be given to subjects.

Advarra recognizes that investigators occasionally face circumstances where: (1) an individual who does not understand English is eligible for an IRB-approved research protocol; and (2) the investigator has an IRB-approved English language long form but does not have an appropriate IRB-approved written translation of the long form. This may occur because neither the investigator nor the sponsor/CRO reasonably expected enrollment of a subject for whom a translation would be needed.

Advarra permits the use of short form consent in appropriate situations. A short form consent is written in a language understandable to the subject and sets out the basic regulatory elements of informed consent.

For some research, the subject enrollment time frame may be sufficient for the preparation and IRB review of an appropriately translated long form. When this is the case, Advarra prefers that the long form be translated and submitted for IRB review. Regardless if the short or long consent form are used, Advarra requires the translation of subject-facing materials.

Advarra prefers that when a short form is used, the investigator promptly obtain a translated copy of the IRB-approved English version of the long form to provide to the subject as soon as possible. This is particularly important for studies with long-term follow-up, as the translated long form is critically important as a means of providing subjects an ongoing source of information understandable to them.

When a long form is not translated for the subject, and there are changes to the research, the investigator is responsible for providing this information to the subject and documenting ongoing consent. This may be done either by (1) verbally obtaining ongoing consent with the assistance of an interpreter, as needed, and documenting this in the subject's study record; or (2) using the same procedure required for initial consent using the short form, as outlined below.

Advarra provides an English short form consent template which meets the regulatory requirements and also has translations of it available in multiple languages. Certified translations of the short form consent are accessible in the Reference Material section of CIRBI. Advarra's IRB has already approved these forms, so when Advarra is the IRB of record for the study no additional IRB approval is required to use these forms to consent non-English speaking subjects. All other short form consents and translations must be submitted for IRB review. If an investigator requires a short form consent in a language not provided in the Reference Material section of CIRBI, the sponsor/investigator may request a certified translation from Advarra.

When consenting a subject using the short form, the IRB must also approve a separate written summary of what the investigator presents orally (with the assistance of an interpreter if the investigator is not fluent in the subject's language). The IRB-approved long form English consent is typically used as the written summary.

Advarra recommends seeking sponsor/CRO approval for use of short forms in multisite studies.

For use of the short form, the requirements are as follows:

- A written summary embodying the basic and appropriate additional elements of consent must be submitted to and approved by the IRB.
- The oral presentation and the short form written document should be in a language understandable to the subject.
- There must be a witness to the oral presentation.
- When the person obtaining consent is assisted by a translator, the translator may serve as the witness.
- If the translator is not serving as the witness, the translator name and /or ID number (for professional translational services providing only a translator ID number) should be documented on the short form along with the signature of the witness.
- The subject or the subject's LAR (if approved by the IRB) must sign and date the short form.
- The witness must sign and date both the short form and a copy of the written summary.
- The person obtaining consent must sign and date a copy of the written summary.
- A copy of the short form and written summary must be given to the subject or the subject's legally authorized representative.

- For research involving children where the IRB requires that both parents/legal guardian provide parental consent, both parents/legal guardians should sign on the signature line.

- HIPAA authorization: Use of a short form consent does not satisfy the requirements for authorization of PHI under HIPAA. The investigator may consult with his or her institution to obtain a translated HIPAA authorization or contact Advarra to obtain a translation.
- ICH-GCP does not allow for use of a short form consent. Therefore Advarra will not normally approve a short form consent for Canadian research; Canadian subjects must sign a translation of the IRB-approved study ICF in a language the subject can read and understand.
- **Studies conducted under the Old Common Rule:** The short form must state that the elements of informed consent required by the regulations (21 CFR 50.25 and 45 CFR 46.116) have been presented orally to the subject or the subject's legally authorized representative.
- **Studies conducted under the Revised Common Rule:** The short form must state that the elements of informed consent required by the regulations (21 CFR 50.25 and 45 CFR 46.116) have been presented orally to the subject or the subject's legally authorized representative, and that the key information required by 45 CFR 46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided.

Please contact Advarra for additional information or assistance with short forms.

7.3. Subject Payments

Regulations require the IRB to ensure that the investigator seeks consent only under circumstances that minimize the possibility of undue influence. Regulatory agencies have provided guidance that certain payment amounts or schedules may create undue influence.

The IRB will permit payment to subjects unless it presents the potential for undue influence. IRB review will focus on whether the payment plan may compromise a subject's evaluation of the risks or may affect the voluntariness of his or her decision to enroll and/or to remain in the study.

Compensation should be based on time invested and inconvenience. It may also be based on types of risks and procedures. However, compensation should not be considered a benefit or a way of offsetting risks.

The ICF should include details on the payment schedule, including the amounts and timing of disbursement (e.g., after each visit, weekly, monthly, etc.). Payment should accrue as the study progresses and not be contingent upon completion of the entire study reimbursement for parking, hotel, transportation, etc. Study reimbursement is not considered compensation and does not raise concerns regarding undue influence.

The investigator is required to inform the IRB of any plans to pay subjects for participation in a research study in the initial submission materials as well as any time payment is modified. The IRB will not approve the investigator/site until the payment amount and timing of disbursement of subject payment is submitted.

If an investigator plans to provide subject payment, subjects should be paid in a timely manner at the end of their participation in the research study. Payment to subjects must not be contingent upon the site's receipt of payment from the sponsor.

While the entire subject payment should not be contingent upon completion of the study, payment of a small proportion at the end of the study as an incentive for completion may be considered acceptable if it is determined to be reasonable and not so large as to unduly influence a subject to stay in the study when they would otherwise have withdrawn. In general, Advarra considers completion bonuses of **no more than 25%** of the total compensation to be acceptable. Compensation to subjects may not include a sponsor coupon good for a discount on the purchase price of the product once it has been approved for marketing.

If the research includes subjects that are minors, the appropriateness of any proposed payments to the parent(s) or guardian(s) and to the minor is also reviewed by the IRB.

7.4. Compensation for Research Related Injury

For greater than minimal risk research, regulations require an explanation as to whether there is any compensation for research-related injury. Also required is an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Additionally, regulations prohibit the use of exculpatory language and require that information given to subjects be in a language understandable to them.

The ICF must describe compensation for subject injury in lay language (no technical or legal language). The description must address compensation for the subject directly, rather than the contractual arrangement between the sponsor and the site. Language may not be exculpatory. Exculpatory language is language which has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt.

Sponsors and investigators must ensure that the description of any compensation or medical treatment that will be provided to a subject or legally authorized representative for a research-related injury does not conflict with any information contained in the contract between the sponsor and the investigator or the investigator's institution.

7.5. Informed Consent Translations

The ICF provided to the subject or legally authorized representative should be written in the language spoken by the potential study subject or legally authorized representative.

If non-English speaking subjects will be enrolled on the study, a certified translation of the IRB-approved ICF must be used. If an investigator plans to enroll non-English speaking subjects, the investigator must contact the IRB prior to non-English speaking subject enrollment to obtain a certified translation of the IRB-approved ICF.

Advarra is able to provide translation services, along with an affidavit of accuracy/translation certificate through a third-party translation vendor, upon request. If a sponsor chooses to use another vendor for the translation, a copy of the affidavit of accuracy/translation certificate, as well as a copy of the translated master ICF in an MS Word compatible format must be submitted to the IRB for release to the site(s).

7.6. Informed Consent for Potentially Vulnerable Subjects

Vulnerable subjects may not be targeted for enrollment into a study unless specifically allowed by the protocol. If the investigator plans to enroll potentially vulnerable subjects, there must be additional procedures/protections in place to protect the rights and welfare of these subjects. Some additional safeguards that may be taken into consideration include:

- An altered informed consent process (e.g., consideration for where the consent process takes place, the persons involved in the consent process, and/or additional information that should be provided to these subjects).
- The need for a LAR or surrogate to provide consent on behalf of a vulnerable subject.
- Study design changes or considerations that would minimize risk for the vulnerable subjects (e.g., removal of identifiers when such subject information is not essential to the research).
- The need for referral assistance for vulnerable subjects (e.g., psychiatric consult/care).

Subjects who may need extra time to decide whether to participate in the study (e.g., seriously/terminally ill or elderly subjects) must be given ample opportunity to involve family member(s) and/or significant other(s) during the informed consent process.

Information about the recruitment of potentially vulnerable subjects and the procedures used to protect their rights and welfare must be reviewed and approved by the IRB before these potential subjects are recruited for the study.

7.7. Informed Consent for Minors

In research studies involving minors, the IRB determines whether assent of the child is required and, if so, how assent should be documented. The assent requirements and the number of parents that must provide permission are communicated in the IRB approval letter.

The minor and the parent(s) or guardian(s) must be given adequate time and an adequate place to read and review the IRB-approved ICF and assent form. The study must be explained to the minor in a language that the minor can understand. The minor must be given an opportunity to ask questions about the study (without the presence of the parent or guardian, if requested and appropriate).

Regulations require the IRB to determine that adequate provisions are made for obtaining assent (agreement) from children to participate in research. Advarra is flexible with respect to client proposals for assent but implements general age guidelines based on an assessment of the capability of children to understand the research and be consulted. Advarra recommends that assent be obtained from participants ages **7** and older.

- Assent from participants younger than **7** is generally not permitted.
- Assent from participants **10** and older is generally required.

Advarra recommends that a separate assent form be used to obtain assent from participants ages **7-13**, and that participants ages **14** and older sign an assent line in the main ICF.

The IRB will review the assent/consent documents in order to ensure that the scope of the information and the language is age-appropriate for the proposed age range.

Note that assent forms do not need to include all elements of consent. However, the main ICF signed by parents/legal guardians must contain all elements.

7.8. Informed Consent for Legally Authorized Representative (LAR) and/or Caregivers

A LAR is used for adult subjects who cannot consent on their own behalf. The process for designating a person as a LAR is determined by state/provincial and local law.

For studies conducted under the Revised Common Rule, if there is no applicable state or local law for allowing a legally authorized representative to provide consent on behalf of a prospective subject, an individual who is recognized by institutional policy as acceptable for providing consent in a non-research setting to the procedures involved in the research will be considered a legally authorized representative for the purposes of research.

A LAR may be required to provide consent in a study where the subject does not have the legal capacity to consent to their participation in the study. If a participant is not able to provide consent, that should not necessarily mean they are precluded from participation in research. A LAR may be an appropriate substitute. However, regulations identify "mentally disabled persons" as a vulnerable category of subjects, and IRBs and investigators should carefully consider whether inclusion of individuals who lack consent capacity is appropriate for the research. Special care is needed when the LAR is reading the ICF because the LAR is giving permission for someone else to participate in a research study.

If a LAR is utilized to provide consent on behalf of a subject, sites must have a written procedure to identify and document who meets the criteria under state and local law to serve as a LAR. The IRB will generally accept the

request for consent by LAR unless there is a justification for why it is not appropriate for the study. Considerations include but are not limited to:

- Protocol eligibility criteria (consent via LAR must generally be explicitly permitted in the protocol)
- Complexity of protocol requirements
- Potential for benefit to the participant
- Whether the research is studying a participant population often requiring LAR (e.g., Alzheimer's)

If the protocol does not allow subjects to be consented with a LAR, and the submission form indicates that a LAR may be used, the approval will include a statement that consent via a LAR is not allowed. To appeal this determination, submit protocol documentation for review and approval.

When research is subject to HHS regulations at 45 CFR 46 subpart B and involves non-viable neonates, the consent of a LAR for either or both of the parents is not permitted.

For DoD funded research, if consent is to be obtained from the experimental subjects' LAR, the research must intend to benefit the individual participant.

A LAR is not always the caregiver. Caregivers are not subjects of a clinical investigation or human subjects unless data is collected about them. There is no regulatory requirement for individuals other than subjects to provide consent for research-related activities, and referring to a "caregiver consent" is confusing with respect to whether the investigators and the IRB are considering these individuals to be subjects. The protocol and ICFs must be clear as to whether caregivers are also subjects themselves.

When caregivers are not subjects (e.g., their role is limited to driving subjects to appointments, assisting subjects with answering questions or with study drug compliance), then it is not appropriate to obtain a commitment from them under a process described as "informed consent" or using a "consent form." Investigators may instead use information sheets, commitment forms, or other documents to solicit agreement from an individual to serve as a caregiver (these may include signature lines). Submission of these types of documents to the IRB is generally not required, but if submitted they will be reviewed to ensure accuracy.

If caregivers are also subjects (e.g., they are answering questions about how they feel as a caregiver), then informed consent is required, and the ICF must include all elements of consent.

7.9. Consent to Autopsy

State/Provincial law governs who can consent to an autopsy for a deceased individual. A person who is alive cannot consent to his or her own autopsy. Additionally, deceased subjects do not meet the regulatory definition of "human subjects."

The ICF may not include language that the participant is being asked to consent to autopsy. If this language is included, the IRB will revise the ICF to state that, if participants pass away, their next of kin may be asked to agree to an autopsy and participants are encouraged to discuss their wishes in advance.

The protocol description of how consent to autopsy will be obtained must be consistent with the ICF. Autopsy procedures may generally remain in the protocol; however, this will be assessed on a case by case basis (e.g., if the focus of the research is on autopsy procedures, this may not be appropriate for IRB review).

7.10. Informed Consent for Non-Reading Subjects

If subjects who are unable to read are allowed by the protocol and approved by the IRB, an impartial witness (i.e., not part of the research team) must be present during the entire informed consent discussion. Once the ICF is read

and explained to the subject, and the subject has orally consented to participate in the research study as well signed and dated the ICF (if capable of doing so), the witness should also sign and date the ICF.

The IRB will incorporate an additional signature block for the witness into the IRB-approved informed consent, if applicable.

7.11. Informed Consent for Non-English Speaking Subjects

The ICF provided to the subject must be written in the language spoken by the potential subject.

If non-English speaking subjects are recruited, a certified translation of the IRB-approved ICF is required. If investigators plan to enroll non-English speaking subjects, they must contact the IRB prior to enrollment to obtain an IRB-approved certified translation.

An individual fluent in the language spoken by the potential study subject must be available during the informed consent process. If an investigator expects to enroll non-English speaking subjects, provisions should be made to accurately communicate study-related information during all subject interactions in a language the subject can understand.

7.12. Informed Consent for Potentially Decisionally Impaired Subjects

Investigators are required to provide a detailed plan when recruiting subjects with psychiatric, developmental, cognitive, environmental, or health conditions that may interfere with the subject's ability to understand and make rational decisions about involvement in a research study.

The investigator or equally qualified designee must assess a potential subject's competency to provide consent for the research. Subjects found to be incompetent to provide consent, or whose competency is in doubt, may not be enrolled into the research study unless the protocol allows for a legally authorized representative (LAR) and that representative is available during the informed consent process. The LAR must provide consent prior to subject participation in the research.

7.13. Waiver(s) of Informed Consent and/or HIPAA

Under certain circumstances, it may be appropriate to waive some or all of the elements of informed consent and/or HIPAA. Questions relevant to these determinations are addressed at the time of initial submission to Advarra.

7.14. Screening ICFs

Consent for screening procedures may be incorporated into the main study ICF. This type of inclusive single ICF is generally the IRB's preference. However, for some studies it may be appropriate not to describe the screening procedures in the main ICF. For example, if the study is very complicated and requires a lengthy consent form, it may be confusing to include the additional screening procedures in that form.

- **Studies conducted under the Old Common Rule:** Consent must be obtained before screening for study eligibility (unless the procedures would have been done for clinical purposes). If a separate screening ICF is used, it must include all of the elements of informed consent. See 21 CFR 50.25 and 45 CFR 46.116 for details on these requirements.
- **Studies conducted under the Revised Common Rule or FDA regulations only:** Information or biospecimens for screening, recruiting, or determining eligibility may be obtained without the informed consent of the subjects if (1) information is obtained through oral or written communication with the subject, or (2) identifiable information or identifiable biospecimens are obtained by accessing records or stored specimens. If screening tools are used (such as telephone screening scripts, online questionnaires, etc.), these require review of the IRB.

FDA provides some helpful guidance on screening tests prior to study enrollment. According to this guidance, an investigator may discuss the possibility of entry into a study with a prospective subject without first obtaining consent, but informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining study eligibility.

Clinical screening procedures for research eligibility are considered part of the subject selection and recruitment process and require IRB oversight. For studies that include clinical screening procedures and plan to use a screening ICF, the screening ICF should focus on describing the study screening procedures and does not need to include complete details about the main study. However, a brief summary of the main study must be included so that participants understand the procedures they will undergo if they are screened into the study. This summary helps explain to potential participants why the screening procedures are being performed, so they can make an informed decision about whether to agree to the screening procedures.

8. Electronic Informed Consent (eConsent or eIC)

eConsent or eIC refers to the use of electronic systems and processes that may employ multiple electronic media (including text, graphics, audio, video, podcasts, passive and interactive websites, biological recognition devices, and card readers) to convey information related to the study and to obtain and document informed consent. For more information on eConsent, reference FDA/OHRP Guidance on Use of Electronic Informed Consent – Questions and Answers.

The IRB supports and encourages the use of eConsent technology for improved human subject protections. eConsent technologies may help research subjects make informed, rational decisions about clinical trial participation by enhancing the way study information is presented.

The IRB is fully eConsent capable and has the experience to help clients navigate the electronic informed consent review process. Advarra has worked with a variety of eConsent vendors/platforms, and our processes are built to complement any platform.

8.1. Submission Requirements

The IRB can manage eConsent review in different ways:

- Review a Microsoft Word version of the informed consent first followed by review of the eConsent.
- Review eConsent only. This may be possible if there is not a Microsoft Word version of the ICF associated with the study.

In either instance, the method must include a format in which the IRB can edit and provide feedback on the informed consent language.

In addition to the standard submission forms, please include the following with the submission:

- eConsent in electronic format **and** instructions that will allow access and review of the eConsent.
    - Per FDA guidance, the IRB must assess usability by viewing all content in the same matter in which a potential subject would view eConsent content.
- Screenshots of all electronic media used, including text, graphics, audio, video, podcasts, passive and interactive web sites, biological recognition devices, and card readers.
    - This includes hover text, embedded education, tests, hyperlinks, and all tiered or appended information.
- Instructions for receiving feedback/edits.

    - Acceptable methods to receive IRB feedback may include: ability to edit within the eConsent software, or non-electronic/Microsoft Word version text provided for in-line mark-up.
- A version number/date assigned to the eConsent material for version control.
    - The final screenshots should include this reference information.

Following submission, Advarra will follow up to request any additional information needed to complete the review.

Following approval of the eConsent layout/content, documentation must be provided to ensure that the final eConsent is equivalent to what was approved by the IRB. Such methods may include an attestation of equivalence provided by the eConsent vendor.

8.2. Site eConsent

Following IRB approval of the template study eConsent, site eConsent submission requirements are as follows:

- Individual site eConsents do not have to be reviewed if the only change to the template eConsent is the addition of the investigator's name/contact information and subject compensation already approved by the IRB. In addition, an attestation of equivalence is not required.
- When a site has site-specific/unique language that differs from the content of the template informed consent document/eConsent, the IRB must review and approve the language.
    - When a Microsoft Word version is used, documentation must be provided to ensure that the approved paper version of the site ICF is equivalent to the digitized eConsent. Such methods may include an attestation of equivalence provided by the eConsent vendor.
    - When there is no Microsoft Word version, the IRB must have a way to review and edit site-specific versions of the eConsent. Documentation must be provided to ensure that the final site eConsent is equivalent to what was approved by the IRB. Such methods may include an attestation of equivalence provided by the eConsent vendor.

8.3. Obtaining Ongoing Approval

The IRB must be able to view changes being made to the eConsent. If the study includes a Microsoft Word version of the informed consent, provide the requested revisions in tracked change mode. If there is no Microsoft Word version, provide the eConsent revisions in a way in which the IRB can identify the revisions (e.g., redline, highlighting, etc.).

Any revisions to media embedded in the eConsent, such as graphics, audio, video, and hyperlinks, must also be submitted separately for review prior to use.

When there is significant new information that would impact a subject's willingness to continue to participate, and there is not sufficient time to update the eConsent, consider submitting for review a Microsoft Word version of the ICF and/or a "dear subject" notification to communicate updates to the subjects in an accelerated manner.

8.4. Remote Consenting

The challenge with remote consenting via eConsent is confirming the potential subject's identity. Documentation of informed consent cannot be waived for FDA-regulated studies, so if an individual's consent needs to be obtained at a distance, we still need a way to appropriately enable an individual's consent. One idea is to use a part 11-compliant eConsent platform robust enough to meet the remote consent criteria, including electronic signature verification. The FDA-OHRP guidance also suggests verifying identity through state-issued IDs, personal security questions, biometrics or visual methods (e.g., webcam).

9. Mobile Apps

A “mobile app” is defined as either a software application that can be run on a mobile platform (i.e., a handheld commercial off-the-shelf computing platform, with or without wireless connectivity) or a web-based software application that is tailored to a mobile platform but is executed on a server.

The use of mobile apps in research is increasingly common. The app may be the sole focus of the research (e.g., app that controls the delivery of insulin through an insulin pump) or may be used as a tool in collecting data for the research (e.g., app that collects patient recorded outcomes through surveys). Mobile apps pose unique regulatory questions for investigators, sponsors, and IRBs, particularly with respect to confidentiality.

The IRB requires the protocol or supporting documentation provide detailed information about what the app does and how it will be used in the research. There must be sufficient data supporting the accuracy of the app and the claims made about how it is intended to work.

Sponsors and investigators must carefully consider the accessibility and usability of the app and whether it is appropriate for the subject population. The protocol should describe what training and ongoing support will be provided to participants in the event they encounter technical challenges. Study termination and withdrawal procedures should address whether subjects will be able to deactivate the app if they decide to withdraw from the study, as well as whether investigators are able to suspend the app remotely should they need to stop the research.

Subjects must be informed of whether they will be provided with mobile devices or if they are expected to use their own devices, and whether they will be responsible for any costs associated with the use of the app (e.g., increased cell phone costs for data use).

As with all research studies, the protocol and ICF must describe the data that will be collected, whether it will be identifiable or de-identified, and how confidentiality will be maintained. This description must include both the data captured by the app for research purposes as well as any incidental data (such as location stamps) that may also be collected.

The data security controls outlined in the protocol should describe how risks of third-party data interception will be minimized, where the data is stored throughout the lifecycle of the research study, password protections, encryption of data stored on the device, encryption of data stored elsewhere (such as the cloud), and encryption of the data in transit.

FDA regulates a subset of mobile apps which meet the definition of “mobile medical app.” A “mobile medical app” is a mobile app that meets the statutory definition of a device and either is intended (1) to be used as an accessory to a regulated medical device, or (2) to transform a mobile platform into a regulated medical device. FDA has stated that the agency intends to exercise enforcement discretion with respect to mobile apps that may meet the definition of a medical device but pose a low risk to participants. Sponsors are responsible for determining whether an investigational device exemption (IDE) application is required for the proposed research, and the IRB requires that IDE information be submitted at the time of initial review.

9.1. Terms of Use (TOU)

Apps or other technology used in research may have “terms of use” that must be agreed to before someone can use the app or technology. Sometimes these documents include information that impacts the regulatory criteria for informed consent.

The IRB will focus on the TOU when it is for a technology that is part of the research (e.g., for a mobile app that is an investigational device, or for a website that is used for surveys).

The TOU is reviewed to determine if ICF edits are needed. For example, the TOU may include specific information on privacy/confidentiality/data sharing that needs to be added to the ICF, or it may contain exculpatory language, which requires inclusion of a statement in the ICF explicitly preserving participants' rights.

10. Registry Studies

Registry studies are observational research studies, usually limited to data collection and do not include procedures or interventions that are being conducted specifically for the research (e.g., randomization or assignment to treatment groups), although a specific treatment may be part of the inclusion criteria. A registry study generally involves collection of data from tests and measurements a medical provider orders as standard of care for monitoring a patient's health. Registry studies may also be required by the FDA as part of post-approval requirements for a drug or medical device.

Study protocols for registry studies should include the purpose for establishing the registry, the data elements collected for the registry, and the data collection time period. If biological specimens are also collected as part of the registry, the protocol should note the types of specimens collected (e.g., whether they are being collected as part of the standard of care), collection time points, and the methods used to collect the specimens. Measures in place to ensure subject privacy and confidentiality of data must also be included in the protocol.

11. Future Research

Many studies will include plans to collect data or specimens for future research. In some cases, the future research is well-defined, and in others it is unspecified. The IRB generally allows the collection of information and specimens for future research, provided that the protocol documentation and ICF include, at a minimum, the following information:

- What diseases/conditions will be the focus of the research
- What types of testing will be conducted (e.g., genetic, creation of cell lines, etc.)
    - If genetic research: whether subjects/investigators will receive results
- Whether the samples will be coded/de-identified
- Who will have access to the samples/data
- How long samples will be stored/how long data will be used (may be indefinite)
- Whether samples/data will be shared with secondary researchers, including submission to public databases (for example: dbGaP)
- Whether the sample/data collection is optional or mandatory, and whether participants may withdraw
    - Note that unspecified future research with identifiable samples must be made optional

The protocol must describe all research, including future research, in sufficient detail for the IRB to make all regulatory requirements, including assessing confidentiality and risk.

The ICF must include all regulatory elements of consent and include sufficient information to enable the subject to understand what they are agreeing to. This information must be supported by the protocol or other protocol documentation; it cannot be solely in the ICF or submission form.

For studies conducted under the Revised Common Rule that involve collection of identifiable private information or identifiable biospecimens, the ICF must describe:

- Whether identifiers might be removed and the information and biospecimens could then be used for future research or provided to another investigator for future research without additional informed consent, **OR**

- (If the first option is not the case) That the private information or private biospecimens collected during the study will not be used or distributed for future research.

12. Genetic Testing

Results of genetic testing can lead to discriminatory actions against an individual. Genetic testing is relevant to the IRB's regulatory determinations regarding risk, and the assessment of confidentiality and privacy measures. Regulations require that the ICF include a description of the procedures to be followed, information about reasonably foreseeable risks (which includes risks to privacy), and information regarding confidentiality. The protocol and ICF must describe any genetic testing to be performed. When genetic testing will be performed, the risks of genetic testing must be included in the ICF. The description should also include information about GINA protections and limitations. Research looking at only specific biomarkers generally does not require genetic testing risks in the ICF.

13. Returning of Individual Research Results

There is no requirement that individual results be returned to subjects, but the IRB does require information about plans for return of results in order to make regulatory determinations regarding risk, benefit, and assessment of confidentiality and privacy measures. Regulations require that the ICF include a description of the procedures to be followed, information about reasonably foreseeable risks (which includes risks to privacy), potential benefits, and information regarding confidentiality. The protocol and ICF must specify if any individual results will be returned to the subject or placed in their medical records. Only a brief description is required in the protocol and ICF, including what information will be returned, who will provide the information, and when the disclosure is expected to take place.

- **Studies conducted under the Old Common Rule**: If individual results will not be returned, the protocol and ICF may state this explicitly or remain silent.
- **Studies conducted under the Revised Common Rule that may have clinically relevant research results:** The ICF must describe whether results that are clinically relevant, including individual research results, will be disclosed to the subject (and the conditions under which they will be disclosed), or, if this is not the case, that clinically relevant research results, including individual results, will not be disclosed to subjects.

14. [Content Removed]

15. Documenting Blood Volume

Regulations require the ICF to describe study procedures, which includes blood tests and reasonably foreseeable risks which may result from blood draws. The ICF must include the number of blood draws.

The protocol must include general information about blood draws but does not need to include details regarding the number of blood draws or volume. Depending on the study design and subject population, the IRB may require information regarding blood draws in order to ensure that risks are minimized.

If the IRB believes that the amount of blood taken is excessive given the number of blood draws, the IRB may ask for **more specific information** relating to the total volume of blood and the justification for a volume that appears to be high given the time period of the blood draws and/or characteristics of the subject population. The critical issue is that the ICF accurately describes for subjects the number of blood draws and that the IRB consider this information in relation to any vulnerabilities of the subject populations.

While there will be case by case issues, generally the issue for the IRB is whether the amount of blood that is drawn is excessive for the research or excessive for the population. If the IRB raises this concern, the IRB will request additional information. For example, the IRB's justification for requesting additional information could be that the subject population is one weakened and fatigued from previous therapies and that the amount of blood drawn as evidenced in the number of blood draws raises concerns as to whether this will be excessive for this population.

The protocol or protocol-related documents do not need to contain these total blood volumes unless the IRB determines and documents that there is a specific reason why it needs to be in the protocol.

16. Research with Vulnerable Populations

16.1. Research with Employees

Employee participation raises potential concerns about undue influence because of the perceived possibility that a decision to participate could affect a participant's employment status. If the protocol targets this population (e.g., employment is part of the eligibility criteria), the IRB will add standard "non-coercion" language to the main ICF. If a site indicates that employees may be enrolled, then the IRB will add standard language to the site's ICF only. The IRB will consider if additional protective measures are necessary, especially where the protocol itself targets employees by design.

16.2. Research with Minors

Children are defined as persons who have not attained the legal age for consent to treatment or procedures involved in research, as determined under the applicable law of the jurisdiction in which the research is conducted. If children are recruited for a study, sites must be knowledgeable about the age of majority as defined by state/provincial and local law and have a process to determine who meets the definition of a child in the respective state or province.

When a minor is legally emancipated from his or her parents, the minor becomes an adult for legal purposes and signs the adult ICF, provided there are no state requirements prohibiting consent to research. An emancipated minor is a legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law (for such purposes as consenting to medical care) but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as being self-supporting and not living at home, marriage, or procreation. State laws and statutes regarding emancipation vary considerably, and sites should confirm how their state defines an emancipated minor and what activities emancipated minors are allowed to consent to on their own behalf.

If a site permits a guardian (i.e., an individual who is not a parent but who is authorized under applicable state and local law) to consent on behalf of a child to a research study, the site must have a process to determine who meets the definition of a guardian in accordance with applicable state and local law and a process to document the legal relationship of the guardian to the child.

When research involving children is covered by FDA or HHS regulations, the IRB must make a pediatric risk assessment and only approve research that satisfies the regulatory criteria for research involving children. The IRB also determines whether assent of the child is required. If the IRB determines the assent of the child is necessary, the IRB also decides how assent should be documented. For more information, see 7.8 Informed Consent for Minors.

The regulations provide criteria for research with children that the IRB considers during review of the research, including component analysis. The IRB documents the regulatory category for the research and communicates this

determination in the IRB approval letter. The regulatory categories for pediatric research projects are defined as follows:

- 45 CFR 46.404/21 CFR 50.51: Not involving greater than minimal risk. The IRB determines if permission of 1 or both parents is required.
- 45 CFR 46.405/21 CFR 50.52: Involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. The IRB determines if permission of 1 or both parents is required.
- 45 CFR 46.406/21 CFR 50.53: Involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition. Permission of both parents is required. If wards are to be enrolled, an advocate must be appointed for each ward.
- 45 CFR 46.407/21 CFR 50.54: Not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Specific approval is required from the FDA Commissioner or HHS Secretary. Research involving children that is not approvable under the published regulatory criteria is referred to the appropriate agency (i.e., FDA, HHS) for additional consideration by an expert panel convened by the agency. Research assigned to this category may not proceed until the appropriate regulatory agency has made a determination.

When the research includes multiple arms or cohorts, such as a placebo or standard of care arm compared to an investigational arm, the IRB must perform a component analysis and analyze each group and make a separate determination as to the risk category. The most stringent risk category will be used when determining the number of parents that are required to sign the parental consent.

16.3. Permission by Parents or Guardians and Assent by Children

Assent is defined as a child's affirmative agreement to participate in research/clinical investigation. Adequate provisions must be made for soliciting the assent of the children when, in the judgment of the IRB, the children are capable of providing assent. When the IRB determines that assent is required, it must also determine whether and how assent must be documented. Investigators are provided an IRB-approved assent form as applicable.

When making a determination about requirements for consent from the parents or guardians of the children, the IRB considers the applicable regulations. A parent is defined as a child's biological or adoptive parent. A guardian is defined as an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care, including participation in research.

The IRB determines if permission of 1 or both parents is required for research projects. For research approved under categories 45 CFR 46.404/21 CFR 50.51 or 45 CFR 46.405/21 CFR 50.52, 1 parent may be sufficient to provide consent. When research studies are approved under categories 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54, both parents must give their permission unless 1 parent is deceased, unknown, incompetent, or not reasonably available, or when only 1 parent has legal responsibility for the care and custody of the child, if consistent with state law. Investigators should follow site policies for determining and documenting when a parent is not reasonably available. For more information, see 7.8 Informed Consent for Minors.

16.4. Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in clinical investigations approved under categories 45 CFR 46.404/21 CFR 50.51 and 45 CFR 46.405/21 CFR 50.52. For clinical investigations approved under categories 45 CFR 46.406/21 CFR 50.53 and 45 CFR 46.407/21 CFR 50.54, wards of the state may only be included if such clinical investigations are:

- Related to their status as wards; or

- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

The IRB requires appointment of an advocate for each child who is a ward of the state for any research approved under these 2 categories. The requirements for advocates include:

- The advocate serves in addition to any other individual acting on behalf of the child as guardian or in loco parentis.
- The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.
- The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the sponsor organization.

1 individual may serve as an advocate for more than 1 child.

The protocol submission must indicate if wards of the state may be enrolled into the study.

16.5. Research with Prisoners

“Prisoner” means 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 (45 CFR 46.303[c]).

Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons or may be untried persons who are detained pending judicial action (e.g., arraignment or trial).

The IRB is constituted to review research involving prisoners. All biomedical and behavioral research that is designed to enroll prisoners (or subjects who are likely to become prisoners) that is conducted or supported by HHS is subject to and reviewed in accordance with the regulations found at subpart C of 45 CFR 46.

For studies that are not designed to enroll subjects who are prisoners or who are likely to become prisoners, the IRB must be notified immediately if a subject participating in a research study at a site overseen by the IRB becomes incarcerated. When notified of an incarceration, the IRB assesses the type of research and advises the investigator as to whether IRB review under subpart C of 45 CFR 46 is required.

For any HHS-conducted or -supported research involving prisoners, the submitting party will certify to OHRP that the IRB reviewed the research and made 7 findings as required by the regulations (45 CFR 46.305[c] and 46.306[a][1]). OHRP will 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. Following its review of the certification, OHRP will send a letter authorizing the involvement of prisoners in the proposed research, if OHRP determines that the research involves one of the permissible categories. Advarra will assist with the certification process.

- **Studies conducted under the Old Common Rule:** The exemption categories do not apply to research involving prisoners.
- **Studies conducted under the Revised Common Rule:** The exemptions do not apply to research involving prisoners, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

16.6. Research with Pregnant Women, Human Fetuses and Neonates

The IRB recognizes that special protections for research involving pregnant women, human fetuses, and neonates apply to research conducted or supported by HHS or conducted at an institution with an FWA under which it has voluntarily agree to apply subpart B of 45 CFR 46 to all research, regardless of the source of support.

For HHS-funded studies, pregnant women and fetuses or neonates may be involved in research if the IRB finds and documents that all of the conditions found in 45 CFR 46.204 or 45 CFR 46.205, respectively, have been met.

Sponsors and investigators should understand the requirements and unique concerns when designing and conducting research studies using this vulnerable population, regardless of the source of funding. Sponsors and investigators are encouraged to contact the IRB for assistance or questions regarding research studies using pregnant women, human fetuses, and neonates.

The IRB will apply subpart B of 45 CFR 46 to all research that involves pregnant women, human fetuses, and neonates. The IRB also apply subpart D of 45 CFR 46 to research that plans to follow outcomes of neonates after viability has been determined following delivery.

16.7. Following Incidental Pregnancies

If a subject who has received an investigational agent gets pregnant, there could be an impact on the fetus and the pregnancy. Sponsors and investigators often want to collect data about the pregnant woman and fetus. Those individuals would then be human subjects and consent is required, as are subpart B and/or D regulatory determinations.

In general, the follow-up activities only involve data collection and are minimal risk activities. The IRB will perform a subpart B assessment when follow up is performed for pregnant participants. The IRB will also perform a subpart D assessment when follow up is performed for newborns after viability has been determined.

As of November 1, 2020, Advarra updated the IRB's policy on the collection of outcome/safety data on pregnant partners of male subjects and newborns born to a subject's partner as follows:

- The collection of outcome/safety data **does not** meet the Department of Health and Human Services (HHS) definition of research because it does not represent a systematic investigation designed to develop or contribute to generalizable knowledge (45 CFR 46.102(l)) and it is not a clinical investigation as defined by the Food and Drug Administration (FDA) (21 CFR 50.3(c)).
- The IRB **will not** make 45 CFR 46 Subpart B or D determinations for follow up of pregnant partners and their children.
- If the protocol states that the collection of data on pregnant partners will occur, the main consent document should inform subjects of the plan to collect this data.
- The IRB **does not** require the submission of additional documents (e.g., a separate informed consent form (ICF) for pregnant partners, authorization form, information sheet, medical release form) to collect outcome/safety data on pregnant partners. If an additional document is submitted, the IRB will review and approve it as subject facing material. If the document is titled informed consent, the IRB will not review the document as a research informed consent form , as pregnant partners of research participants are not considered research subjects and, therefore, the elements of informed consent (45 CFR 46.116(b)/21 CFR 50.25) do not apply. The IRB will not request the submission of these forms.

16.8. Birth Control & Pregnancy Testing Requirements

In some research, taking an investigational agent could be damaging to a fetus. Subjects should be informed of these risks and should be provided with sufficient information to ensure that they are able to make an informed decision regarding participation in the research and their use of contraception. Where the study drug is known to be teratogenic, additional IRB requirements beyond those listed below may be appropriate.

The ICF must provide participants with information about risks to a pregnancy and information needed to make decisions regarding contraception use. Reasonably foreseeable risks to a pregnancy must be included in the ICF. The ICF must also include information regarding the length of time that contraception should be used and/or that the study drug is expected to stay in the body and may affect a pregnancy. This should be based on information in the IB, prescribing information, and/or protocol. It is not required that the protocol include this information. The types of acceptable contraception do not need to be listed in the protocol or ICF. The ICF may instead state that participants should discuss contraception with their study doctor. If the ICF does address specific forms of contraception, this does not need to be supported by the protocol.

If the protocol does address specific forms of contraception, this must be included in the ICF or other documents provided to participants.

Sperm donation limitations are not required to be specified in the protocol. If they have been included in the ICF, they may remain, even without supporting protocol documentation.

In general, the protocol does not need to include definitions for “women of childbearing potential” or “post-menopausal.” Instead, assessment regarding the status of female participants as it relates to these terms may be subject to investigator discretion. If the protocol does include definitions for these terms, the IRB will only require changes if the definitions raise safety concerns or do not appear to have sufficient scientific basis.

Any pregnancy testing conducted as part of the research must be described in the protocol and ICF. The IRB will generally not require testing during the course of the study but will often require testing prior to dosing.

17. Changes in Research Activity Following IRB Approval

17.1. Modifications/Amendments

Changes in research activities must be submitted to the IRB for review and approval prior to implementation, except when necessary to eliminate immediate hazards to subjects. If changes are made to eliminate immediate hazards, the IRB must be promptly notified (for more information, refer to 18.4 Unanticipated Problems). All changes in research activity must contain adequate information for IRB review.

Changes in research activity include but are not limited to:

- Amendments and modifications to the protocol, ICF, investigator’s brochure, and other study documentation
- Changes at the investigational site
- New information regarding the study therapy(ies)

Changes in study status (including any change in the regulatory approval status of the test article, any FDA clinical hold, and any study hold/suspension or termination imposed by the sponsor/CRO, investigator, other reviewing IRB, other government agency, or other party)

When submitting amendments/modifications to any study-related document that requires IRB review, a summary of changes and/or a rationale and a tracked change version of the document should also be included to facilitate a timely review. When ICF changes are requested, those changes must be made and tracked in the most current IRB-approved version of the ICF(s).

17.2. Dose Escalations & Dose Levels in Consent Forms

The IRB needs to assess the doses and the criteria for escalation in order to make regulatory determinations regarding risk. If there is not sufficient information at the time of initial review to make these assessments for the entire study, then IRB approval will be limited to a portion of the study only, and the IRB will need to make the determinations for later phases of the study when complete information is available.

During initial review, the IRB will review the study and ensure that the maximum dose and criteria for escalating are clear and appropriate. If there are issues, these will be addressed at the time of initial review (most likely resulting in deferring the study).

There may be situations where the maximum dose/criteria for escalation is not identified at the time of initial review. In these cases, the IRB will require a protocol amendment to be submitted during the course of the study. This will be clearly stated on the approval letter.

ICFs do not usually need to include specific doses, as that level of detail is not typically necessary for participants to make an informed decision about participating in the research. In general, the IRB will not require specific doses to be included in the ICF. However, there may be situations where the IRB will require more detailed dosing information (e.g., if the study is comparing 2 different doses of the same drug, or when a higher dose is being used than usual for an approved drug). Additionally, if dose information is included in the risk section (e.g., “In studies where participants took the 10mg of study drug, the following risks were seen”), then the ICF should also specify the dose participants will receive so that the risk information is meaningful to them.

If the dose level is included in the consent form, the IRB will generally not require that it be removed, but the information provided to participants must be accurate. Note that the IRB requires dose information to be included in the protocol.

17.3. Clinical Holds and Suspensions or Terminations

Any IRB notification of FDA Clinical Hold or other study hold/suspension or termination imposed by the sponsor/CRO, investigator, other reviewing IRB, other government agency, or other party, must include a summary of the reason(s) for the hold/suspension/termination and provide the IRB with adequate information to assess the impact to the study subjects.

The IRB must be notified when an FDA Clinical Hold, or any other study hold/suspension, is lifted. IRB notification should include a summary of how the issue(s) was resolved and any modifications made to study documents as a result of issue resolution, as applicable (e.g. protocol amendment).

17.4. Change of Investigator/Site Status

The IRB must be notified prior to replacing the current IRB-approved investigator at a site. The new investigator’s CV and the reason for changing investigators must be included with the submission.

Submission to the IRB is also required when the IRB-approved investigator goes on a leave of absence, during which he or she will no longer retain responsibility as investigator and he or she is replaced by a new investigator.

The investigator must promptly report any pending or ongoing legal, regulatory, or professional actions or restrictions related to the practice of medicine or research at the site(s) (including sub-investigators, and site personnel). This information is required at the time of initial submission and post-approval as applicable.

The IRB should be promptly notified in the event the sponsor becomes aware (e.g., during a monitoring visit) of any unanticipated problems, evidence of serious or continuing noncompliance, scientific misconduct, undue influence on the conduct of the study, or any other event that may impact subject safety or alter the IRB's approval or sponsor's/sponsor's representative's status of the investigator/site.

18. Prompt Reporting Events (including Serious Adverse Events, Unanticipated Problems, Protocol Deviations, Violations, or Exceptions, and Noncompliance)

18.1. Serious Adverse Events (SAEs)

Investigators are required to submit any serious adverse events involving subjects enrolled at the site(s) that are determined to be **unexpected** and probably, possibly, or definitely **related** to the test article or research procedures. This notification to the IRB must occur promptly and no later than 2 weeks (10 business days) from the time the investigator learns of the event.

Note: *SAEs that have been determined to be unrelated to the test article should **not** be submitted to the IRB. In addition, for those SAEs where relatedness has not yet been determined (i.e., further analysis is required), submission to the IRB should only occur once it has been determined that the SAE was related to the test article.*

A serious adverse event that is expected, as identified in the study documentation (e.g., product information, protocol, and/or ICF), but is occurring at greater frequency or severity should be reported to the IRB as an unanticipated problem.

Investigators are expected to provide the IRB and sponsor with any additional requested information regarding SAEs, including follow-up reports, autopsy reports, and medical reports.

In addition, investigators are expected to report adverse events and other findings identified in the protocol as critical to safety evaluations, to the sponsor in accordance with the sponsor's reporting requirements and within the specified timeframe.

18.2. External Serious Adverse Events/Unexpected Adverse Device Events (Including IND Safety Reports)

External SAEs (e.g., IND safety reports, suspected unexpected serious adverse reactions or SUSARs), which are SAEs that occur at sites not under the purview of the IRB, should only be submitted if they meet the criteria of an unanticipated problem. Please refer to 18.4 Unanticipated Problems below to determine which external SAEs may qualify for an unanticipated problem involving risks to subjects or others that must be reported to the IRB.

Sponsors and investigators are encouraged to review FDA's Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection.

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated

serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3[s]). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150[a][1]).
- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46[b], 21 CFR 812.150[b][1]).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

Prior to submitting copies of any safety report or UADE report to the IRB, investigators should confirm that the reports have not been submitted on their behalf by the sponsor.

When SAEs or safety reports that do not meet the unanticipated problem or UADE criteria are submitted to the IRB, the submitting party will receive acknowledgement of receipt only and the item will not be reviewed by the IRB. When these items are submitted by a sponsor or CRO, Advarra's default process is to generate an acknowledgement of receipt to all open sites and fees apply. If the sponsor/CRO does not wish to send a mass acknowledgement to all sites, they must opt out of this feature.

18.3. Protocol Deviations, Violations, or Exceptions

An investigator may not initiate a change in research activity without IRB approval unless the change is necessary to eliminate apparent immediate hazards to human subjects, in which case it should be reported to the IRB as an **unanticipated problem**.

Investigators and sites must notify the IRB in writing of any unapproved protocol deviations/violations (an accidental or unintentional change to the IRB-approved protocol) that, in the investigator's judgment, potentially caused harm to subjects or others, indicates that the subjects or others are at an increased risk of harm, or has adversely impacted data integrity. Unplanned or unintentional deviations are to be reported to the IRB as **unanticipated problem** or **noncompliance** as noted in 18.4 Unanticipated Problems and 18.5 Noncompliance.

This notification to the IRB must occur promptly and no later than 2 weeks (10 business days) from the time of identification of the unplanned or unintentional protocol deviation/violation. An automatic acknowledgement will be sent from CIRBI and no additional action is required, unless investigators are contacted by the IRB to provide further information.

There are many unplanned or unintentional violations/deviations or changes in study status that do not cause harm, place subjects at increased risk of harm, or adversely affect data integrity. The IRB does not require that these minor violations/deviations be reported. Examples of minor violations/deviations that do not need to be reported may include the following:

- Out of window visits
- Study procedures conducted out of timeframe
- Subject failure to initial each page of the ICF (as applicable)
- Subject failure to return subject materials (e.g., diaries, journals, etc.).
- Administrative hold on a study not related to safety issues

Examples of accidental or unintentional protocol violations/deviations that must be submitted to the IRB include:

- Changes necessary to eliminate apparent immediate hazards to the subject
- Failure to document informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to report serious adverse event to the IRB and/or sponsor
- Failure to perform a required lab test that, in the opinion of the investigator, may affect subject safety or data integrity
- Drug/study medication dispensing or dosing error
- Study visit conducted outside of required timeframe that, in the opinion of the investigator, may affect subject safety
- Failure to follow safety monitoring plan
- Missing or unreturned investigational product

On occasion, an investigator may want to intentionally deviate from the IRB-approved protocol for an individual research subject (i.e., protocol exception). The investigator must get sponsor approval and obtain prospective IRB approval. The planned protocol exception cannot be initiated until the sponsor **and** the IRB have approved the deviation. Furthermore, to the extent investigators or sponsors request protocol exceptions for multiple research subjects, the IRB may determine that a protocol amendment/modification to the IRB-approved protocol is the appropriate course of action.

18.4. Unanticipated Problems

The IRB requires that sponsors and/or investigators/sites (as appropriate) submit in writing any unanticipated problems (UAPs) involving risks to subjects or others, including adverse events that should be considered UAPs as described below. Notification to the IRB of a UAP must occur promptly but no later than 2 weeks (10 business days) from the time of identification.

UAPs are defined as any incidence, experience, or outcome that is:

- Unexpected (in terms of nature, severity, or frequency) given the information provided in research-related documents and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

The IRB uses the following criteria to determine whether an incidence, experience, or event is a UAP involving risk to subjects or others:

- Unanticipated or unexpected at the time of IRB approval;
- Involved new or increased risk to subjects or others; and
- Related to the research.

Examples of the types of adverse events (AEs) that must be promptly submitted to the IRB (regardless of whether they occur during the study, after study completion, or after subject withdrawal or completion) may include but are not limited to the following:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure, such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome.

- A single occurrence, or more often a small number of occurrences, of a serious unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be a UAP.
    - A determination should be made as to whether the series of AEs represent a signal that the AEs were not just isolated occurrences and involve risk to human subjects.
- An AE that is described or addressed in the research-related documents (i.e., investigator's brochure, protocol, ICF) but occurs at a specificity or severity that is inconsistent with prior observations.
- A serious AE that is described or addressed in the research-related documents, but for which the rate of occurrence is a clinically significant increase in the expected rate of occurrence for the study.
- Any other AE that would cause the sponsor to modify study-related documentation or would prompt the IRB to take an action to ensure the protection of human subjects, such as:
    - Any event that requires prompt reporting in accordance with the protocol or sponsor.
    - Any accidental or unintentional change to the IRB-approved protocol that involved risks or has the potential to recur.
    - Any change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
    - Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
    - Any complaint by a subject that indicates an unanticipated risk or which cannot be resolved by the research staff/sponsor.
    - Any other event that may impact subject safety.

The IRB notifies the appropriate regulatory agency of any incidence, experience or outcome that the IRB has determined to be a UAP involving risks to subjects or others.

The investigator is responsible for the documentation, investigation, and follow-up of all unanticipated problems that occur at the site in which the investigator is responsible for the conduct of the research.

Sponsors must also report any unanticipated problems that occur at sites outside of the IRB's jurisdiction which are relevant to the sites that are under the IRB's jurisdiction.

If there are questions about unanticipated problems involving risk to subjects or others, please contact the IRB.

18.5. Noncompliance

Investigators/sites and sponsors are expected to comply with applicable regulations and IRB determinations/requirements when conducting research. Noncompliance with the regulations and/or IRB determinations and requirements can result in an action up to and including suspension or termination of IRB approval.

The IRB defines noncompliance as any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with applicable regulations, the IRB's *Handbook*, and/or the determinations and requirements of the IRB. Noncompliance may range from minor to serious; be unintentional or willful; and may occur once, sporadically, or continuously. The degree of noncompliance is evaluated on a case-by-case basis and takes into account whether subjects were harmed or placed at an increased risk of harm.

Serious noncompliance is defined as any action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risk to subjects, or compromises the scientific integrity or validity of the research.

Continuing noncompliance is defined as a pattern of repeatedly failing to comply with applicable regulations, the IRB's Handbook, and/or the determinations and requirements of the IRB that may affect subjects' rights and welfare, increase risk to subjects, or may compromise the scientific integrity or validity of the research. Continuing noncompliance also includes frequent instances of minor noncompliance or failure to respond to a request to resolve an episode of noncompliance.

Sponsors, investigators and/or research staff must notify the IRB in writing of any instance of noncompliance with the regulations, this Handbook, and/or determinations and requirements of the IRB. This notification must be as soon as possible but no later than 2 weeks (10 business days) from the time of the event.

Any allegation of noncompliance should also be promptly reported via telephone or in writing to the IRB so that a thorough investigation can be conducted. Noncompliance reports or allegations should include the following information (as appropriate):

- Name of the submitting party
- CIRBI assigned protocol number
- Protocol title
- A description of the event
- The impact on subject safety (if any)
- The immediate action(s) taken to ensure subjects were not harmed
- A corrective action plan to prevent re-occurrence
- Non-compliance assertion
- Timetable of events
- Supporting information from other sources (e.g., sponsor) (if applicable)

Reports and allegations of noncompliance will be evaluated by the IRB and can result in an action up to and including suspension or termination of IRB approval. Any report of noncompliance determined by the IRB to be serious or continuing or determination to suspend or terminate IRB approval will be reported to the appropriate regulatory agency by Advarra.

18.6. Site Visits and Observing Informed Consent

The IRB has the authority to observe or have a third party observe the consent process and the research. If concerns about subject safety arise, or when other issues of noncompliance warrant such action, the IRB may conduct site visits or designate an authorized third party or third parties to observe the informed consent process and the research. The IRB may review study records and the site's written operating procedures to assure the integrity of the records and the protection of the rights and welfare of the study subjects.

The IRB may determine that submission of a copy of a subject's signed ICF is required in order to verify that the site is using the correct version of the document. If this determination is made, the IRB notifies the investigator, and the investigator is then responsible for submitting a complete copy of the subject's signed ICF to the IRB.

19. Continuing Review

The IRB determines the frequency of continuing review for the protocol and investigator's/site's conduct of the protocol at the time of initial approval.

Notification of an upcoming continuing review and the information required for submission to the IRB (i.e., report on the progress of the research) is communicated to the submitting party and/or the investigator well in advance of the submission deadline. Every effort is made to notify the sponsor and/or investigator that a continuing review report is

due, however, it is the sponsor's and/or the investigator's responsibility to ensure that continuing review materials are submitted in a timely manner. Delays in providing the required documentation can jeopardize IRB approval. Without continuing review and approval, all study-related activities must stop unless continued participation is approved by the IRB to ensure subject safety.

- **Studies conducted under the Old Common Rule:** The frequency of continuing review may be changed at the discretion of the IRB; however, it shall be no greater than 12 months. Continuing review activities must continue as long as the research remains open to long-term follow-up of subjects, even when the research is permanently closed to new enrollment and all subjects have completed all research-related interventions, or when the remaining research activities are limited to the collection of private identifiable information.
    - For studies conducted under an FWA, continuing review activities must continue in accordance with the criteria stated above and until all data analysis of identifiable private information is complete.
- **Studies conducted under the Revised Common Rule**: Continuing review is not required for research that is (1) eligible for expedited review; (2) exempt research that received limited IRB review; (3) research that has completed all interventions and now only includes analyzing data, even if the information or biospecimens are identifiable; and (4) research that has completed all interventions and now only includes accessing follow-up clinical data from clinical care procedures.
    - However, the IRB may determine that continuing review is required even if a study meets these criteria, as long as it documents the rationale for the decision.

20. Protocol and Site Expiration

If the IRB has not reviewed and approved continuation of a research study and/or investigator by the expiration date, the research must stop unless the IRB finds that it is in the best interest of individual subjects to continue participating in the research intervention(s) or interactions. Without obtaining prior IRB approval, investigators may only initiate changes to the research, including continuing research activities, when necessary to eliminate apparent immediate hazards to subjects. Enrollment of new subjects cannot occur after expiration of IRB approval.

If the investigator wishes to continue to conduct a study for which IRB approval has expired, the following documentation must be submitted within 30 days of expiration:

- Complete continuing review information
- Supporting documentation (as appropriate)
- Rationale for not providing complete information to the IRB in a timely manner
- Corrective steps in place to prevent future delays

If received within 30 days of expiration, the IRB reviews the continuing review information for the referenced protocol and/or investigator. Research activities may not resume until the IRB approval documentation is issued.

If the required continuing review documentation is not received within 30 days of study expiration, the IRB requires a complete protocol and/or investigator re-submission for review.

21. FDA/OHRP or Other Regulatory Audits

Investigators and sponsors under the IRB's oversight must notify the IRB of any inspection reports, FDA Form 483s, warning letters, Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letters, or actions taken by any regulatory agency (e.g., local, state, or federal) including legal or medical actions that occur. This notification must occur promptly via CIRBI and no later than 2 weeks (10 business days) from the time of the event. If

the investigator or site received an FDA Form 483 and/or warning letter, any responses to the FDA must be included with the notification. If the investigator or site did not respond to the FDA, the investigator must provide a written explanation to the IRB of the corrective actions put into place at the site(s) to address any finding(s).

Inspections/audits with no findings do not require submission to the IRB.

In addition, Advarra reports to AAHRPP within 48 hours after Advarra becomes aware of:

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

22. After Completion of the Research

22.1. Termination Notification

The federal regulations require that the IRB be notified of all changes in research activity. Study termination (closeout) is considered a change in research activity which requires reporting to the IRB. Investigators and sponsors must notify the IRB when all research-related activities are complete and there are no active subjects participating in the research. This termination notification is required even if there were no subjects enrolled in the study. The termination submission includes questions about enrollment activities and problems encountered during the conduct of the study.

The IRB will send the investigator(s) and sponsor notification of study termination. Sponsors will not receive a notification of termination until all sites have submitted a termination report and received official notification from the IRB. The IRB considers a study closed (and archived) when all IRB-approved sites have been terminated, and the sponsor has submitted a termination report and received an official notification of termination from the IRB.

All terminated studies are archived in accordance with regulatory requirements.

22.2. Final Reports After Study Completion

Based on applicable regulatory requirements, the investigator should provide the IRB and applicable regulatory authority with a summary of the study's outcome and any required reports upon completion of the study.

22.3. Study Records Archiving

Based on regulatory requirements, Advarra will retain study records for at least 3 years after the last site reviewed by the IRB has terminated. Any hardcopy documents will be moved to the Advarra archive files at termination. After the record retention period has been met, all study-related materials are destroyed.

Once a study is terminated in CIRBI, the study is automatically archived in the system for the retention period noted above. Prior to purging study documentation/information from CIRBI (i.e., studies that have met the retention period), CIRBI sends out an automated notification to the study contacts. The notification instructs the study contacts to log in to CIRBI and retrieve any documentation/information needed within 30 days of the notification. After the 30-day period, all documentation/information is purged from CIRBI.

23. Changes in Regulatory Landscape

23.1. Changes to the Common Rule

As noted in 1.1 Regulatory Changes (Common Rule Changes Effective January 21, 2019), HHS issued revisions to the Common Rule, which were originally published in the Federal Register on January 19, 2017 (82 FR 7149). Changes to the Common Rule are intended to modernize, simplify, and enhance oversight for human subjects research. These changes include revised informed consent requirements, exemptions for certain types of secondary research, and elimination of continuing review for minimal risk studies. The initial effective date for most provisions of the Final Rule was **January 19, 2018**. However, that effective data was delayed twice, and the final effective date became **January 21, 2019**. Where applicable in this Handbook, we have described the differences between studies conducted under the Old Common Rule and studies conducted under the Revised Common Rule.

23.2. EU General Data Protection Regulation (GDPR)

The European Union's General Data Protection Regulation (GDPR) replaces the existing EU Data Protective Directive. It became effective on May 25, 2018 and establishes and enhances protections for the privacy and security of personal data about individuals within the EU. It places restrictions on handling personal data and delineates the responsibilities and obligations of companies processing personal data. It applies directly to companies located in the EU, Iceland, Liechtenstein and Norway (collectively called the EU in this guidance). The GDPR is intended to cover EU personal data, including data processed for clinical trials.

The category of personal data covered under the GDPR is broader than protected health information covered by HIPAA or identifiable private information included in the Common Rule. Under the GDPR, personal data is "any information relating to an identified or identifiable natural person" (the "data subject"). An identified person is someone who can be identified, directly or indirectly, through the following identifiers: name; an identification number; location data; online identifier; or by 1 or more factors specific to the physical, physiological, genetic, mental, economic, cultural, or social identity of that person. The GDPR further defines special categories of data, called sensitive personal data, which are subject to stricter regulation. This would include data typically collected in a clinical trial, including health data, genetic data, and biometric data. This category also includes racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership, sex life, or sexual orientation.

The GDPR applies to data collected and processed in clinical trials conducted in the EU. It also applies to the processing of personal data by a controller or processor not located in the EU when the data processing is related to (a) offering goods or services to subjects in the EU, or (b) the monitoring of behavior of subjects while in the EU. It applies to anyone while in the EU, not just EU residents. **This means that the GDPR may affect US clinical trials even if the trial is not conducted in the EU.**

For example, if a US citizen enrolls in a clinical trial in the US and travels to the EU, all personal data collected and transferred (e.g., from a wearable device or mobile phone collecting health information) to the US while the subject is in the EU is subject to the GDPR. The GDPR generally will not apply to EU citizens enrolling in a US clinical trial while in the US. However, if the clinical trial is being advertised in the EU, or subjects are followed, or follow-up care is provided when subjects return to the EU, then the GDPR may apply.

Reconsent is not required for the use of data collected prior to May 25, 2018, provided that the way the consent was given is in line with the conditions of the GDPR. **In general, where the client does not require that current/former participants be reconsented, Advarra's IRB will not require reconsent.**

The sponsor is responsible for determining whether the study must comply with the GDPR. If the study is subject to the GDPR, detailed data privacy information must be provided to subjects. This may be included in the ICF, a data

privacy addendum, letter to subjects, or other formats as determined by the sponsor (collectively referred to as the data privacy notice). It is likely that the sponsor will have their own template for their data privacy notice.

Sponsors/investigators should inform the IRB whether the GDPR applies to their trial. When it applies, the IRB will confirm that the following data privacy requirements have been included in the data privacy notice:

- Identity and the contact information for the sponsor (data controller)
- Contact information for the data protection officer (if there is one)
- Special categories of personal data that will be collected for the study
- Data privacy rights
- Transfer of data
- Retention of data

Safety reports and adverse event reporting is not subject to GDPR requirements. The GDPR does not require signed written consent for data processing, even for the processing of special categories of data typically collected in a clinical trial.

For now, Advarra will to rely largely on the sponsor/investigator to include the required GDPR data privacy information in the ICF/privacy addendum when it applies. We anticipate that this area of regulation will evolve over the next year and will revise this guidance accordingly.

Abbreviations

The following abbreviations are utilized throughout this document. Please see specific sections of the Handbook for more information.

Abbreviation	Definition
AAHRPP	Association for the Accreditation of Human Research Protection Programs
AE	adverse event
CDPR	California Department of Pesticide Regulation
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CIRBI	Advarra Center for IRB Intelligence Platform
CoC	Certificate of Confidentiality
COI	conflict of interest
CRO	contract research organization
CV	curriculum vitae
DMC	data monitoring committee
DoD	Department of Defense
DSMB	data safety monitoring board
e.g.	exempli gratia (Latin), “for example”
eConsent	electronic informed consent (also known as eIC)
eIC	electronic informed consent (also known as eConsent)
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
FWA	federalwide assurance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HRPO	human research protection officer
HRPP	human research protection program
HSRB	Human Studies Review Board
HUD	humanitarian use device
i.e.	id est (Latin), “in other words”
IAA	IRB authorization agreement
IB	investigator brochure
IBC	institutional biosafety committee
ICF	informed consent form
ICH	International Conference on Harmonization
IDE	investigational device exemption
IND	investigational new drug
IO	institutional official
IORG number	IRB organization number
IRB	institutional review board
LAR	legally authorized representative

MSA	master service agreement
NIDPOE	Notice of Initiation of Disqualification Proceedings and Opportunity to Explain
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
PCP	primary care physician
PHI	protected health information
SAE	serious adverse event
QC	quality control
SMO	site management organization
SUSAR	suspected unexpected serious adverse reaction
UADE	unanticipated adverse device effect
UAP	unanticipated problem
US	United States

REVISION HISTORY

Version 01 Effective on 07-Oct-2019
Updated for Regulatory Changes (Common Rule Effective January 21, 2019)

Version 02 Effective on 29-Nov-2019
Updates: Electronic Informed Consent; Section 8.1 Submission Requirements and 8.2 Site eConsent - updated for clarity

Version 03 Effective on 19-Oct-2020
Version updated to include conflict of interest language.

Version 04 Effective on 09-Nov-2020
See summary of changes for details on changes to this version v11.9.20.

DOCUMENT ELECTRONIC SIGNATURES

DOCUMENT APPROVAL WORKFLOW

Author Approval

Judith Carrithers	I am the author of this document. *Signed 9:05:33 PM UTC 05-Nov-2020*

Required Workflow Steps for this Category

Lauri Carlile *Advarra / Operations Approval*	I have reviewed and approve this document. *Signed 9:09:35 PM UTC 05-Nov-2020*
Michele Russell Einhorn *Advarra / Institutional Official Approval*	I have reviewed and approve this document. *Signed 3:32:44 PM UTC 06-Nov-2020*