

Principal Investigator Responsibilities Handbook

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Introduction

The principal investigator of the research study is ultimately responsible for the conduct and supervision of a research study and the informed consent process. The principal investigator is responsible for compliance with Department of Health and Human Services (DHHS) Federal regulations, Food and Drug Administration (FDA) regulations, his/her state and local laws, and Goodwyn IRB's policies and procedures. Please review Goodwyn IRB's requirements (Terms of IRB Oversight and Protocol Commitments) in the Investigator Application and this summary of responsibilities carefully.

As a general condition for the approval of a research study, the principal investigator of the study is responsible for ensuring that:

- 1) Voluntary informed consent is obtained from each prospective human research subject, or his/her legally authorized representative, using only the approved consent forms bearing a current Goodwyn IRB "Approved" stamp.
- 2) Human research subjects are kept fully informed of any new information that may affect their willingness to continue to participate in the research study.
- 3) The privacy of human research subjects is protected and the confidentiality of data is maintained. **[See "Privacy and Confidentiality", page 8].**
- 4) Unanticipated problems involving risks to participants and others including unexpected and related adverse events are reported to Goodwyn IRB as soon as possible after the principal investigator (PI) learns of the event, but in all cases within 10 working days.

Specific Responsibilities of Study Investigators

Investigator Responsibilities

The principal investigator of an approved research study is responsible for:

- 1) Responding to all requests for information or materials solicited by the IRB within the time frame requested, including the submission of the research study for periodic review or renewal.
- 2) Abstaining from the enrollment of any individual in a research study (i) until such study is approved in writing by the IRB; (ii) during any period wherein the IRB or sponsor/principal investigator has suspended study activities; (iii) following IRB - or sponsor/principal investigator-directed termination of the study; or (iv) if site approval has expired.
- 3) Ensuring that all associates, colleagues, and other personnel assisting in the conduct of the research study are fully informed of (i) the study procedures; (ii) informed consent requirements; (iii) the vulnerable population(s) subject to study or likely to be enrolled; (iv) the special measures that must be followed when enrolling a vulnerable subject **[See "Vulnerable Subject Populations" page 5];** (v) the potential adverse events associated with study participation and the steps to be taken to reduce potential risks; (vi) adverse event reporting requirements; and (vii) data collection and record-keeping criteria.

- 4) The principal investigator is responsible for providing adequate supervision of those to whom tasks are delegated and the principal investigator is accountable for violations resulting from failure to adequately supervise the conduct of the study.
- 5) Conducting the study in strict accordance with the current IRB-approved research protocol.
- 6) Obtaining and documenting informed consent using the current IRB-approved informed consent process and document(s) prior to conducting any study procedure.
- 7) Requesting and receiving IRB approval for any recruitment / retention / study materials prior to using such materials. **[See “Recruitment / Retention and Other Written Materials for Subjects”, page 10].**
- 8) Requesting and receiving IRB approval of any proposed modification to the research, informed consent document(s) and any recruitment / retention / study materials prior to implementing such modifications.
- 9) Informing the IRB about changes in personnel assisting in the conduct of the research study.
- 10) Reporting to the IRB events that may represent unanticipated problems involving risks to participants and others including unexpected, related adverse events. Researchers are required to submit the report as soon as possible after the investigator learns of the event, but in all cases within 10 working days. **[See “Reporting Responsibilities of Study Investigators”, page 9].**
- 11) Ensuring that, in the event of an adverse event, every reasonable effort is made to provide the involved research subject with adequate care to correct or alleviate the consequences of the adverse event to the extent possible. **[See “Research Study Tasks that the Principal Investigator Cannot Delegate”, Page 4].**
- 12) Ensuring that human research subjects are kept fully informed of any new information that may affect their willingness to continue to participate in the research study.
- 13) Maintaining adequate, current, and accurate records of research data, outcomes, and adverse events to permit an ongoing assessment of the risk/benefit ratio of study participation.
- 14) Consulting with local counsel to ensure compliance with state and local laws.

State/Local Laws Impact Clinical Research

Health practitioners (investigators) who conduct clinical trials under state licensure must be compliant with state laws to maintain that licensure. Investigators must know the state and local laws relative to a research study. If you are uncertain, you must contact your local counsel.

Major Legal Areas:	Examples include, but are not limited to:
<i>Informed Consent</i>	Age of consent Effective time period Definition of legally authorized representative Specific requirement for research consent

	<p>Additional consent requirements for HIV/AIDs testing</p> <p>Additional consent requirements for genetic testing.</p> <p>Additional consent requirements for special populations (i.e., mental disorders, prisoners, youths in detention centers, nursing homes, disabled persons, etc.)</p>
Clinical Research Conduct	<p>Submission to state authorities</p> <p>Insurance reimbursement for standard of care procedures done during a clinical trial</p> <p>Delegation of study tasks to site personnel – what tasks can be delegated to whom depending upon personnel’s licensing and qualifications</p> <p>Investigator registration / licensure for research with controlled substances</p>
Investigational Drug Handling	<p>Special labeling for certain investigational drugs</p> <p>Specific requirements for where drug can be stored</p> <p>Specific requirements for who can prepare / dispense drug</p> <p>Special requirements for state reporting about the investigational product</p>
Other	<p>Laws Governing IRBs</p> <p>Genetic Research</p> <p>Medical Records Privacy / STD Reporting</p> <p>Gifts to Research Personnel</p> <p>Etc.</p>

The information presented here does not constitute legal advice and should not be used as a substitute for legal counsel.

Research Study Tasks that the Principal Investigator Cannot Delegate

The principal investigator must 1) ensure that adequate medical care is provided to subjects for any adverse events related to a research study, and 2) must provide for appropriate medical evaluation and treatment until resolution of any condition related to the study intervention that develops during the course of a subject’s participation in a research study. The principal investigator cannot delegate these responsibilities.

Principal investigators must be available by phone or other electronic communication, and in reasonable close proximity to study subjects, for the duration of a research study. If it is necessary for a principal investigator to be unavailable for a period during the study, clinical responsibility can be delegated to a qualified sub-investigator. If the sub-investigator to whom this responsibility will be delegated is new to the study team, s/he must be submitted to the IRB for review and approval before its implementation.

Primary Care Physician as Investigator

When the Primary Care Physician (PCP) also serves as the investigator in a clinical research study, special considerations arise. Patients have an ongoing relationship of trust with the PCP and may not exercise the same degree of independent judgment they would ordinarily in determining whether to participate in a clinical trial. In this context, certain measures may help to encourage the patient’s independent consideration and to reduce the PCP’s influence in recommending the study just by virtue of his/her participation as the PI. The best way to address this situation will depend on the investigator’s office and the patient’s own resources. These measures may include any of the following:

- Having a friend or family member present during the informed consent process (ICP)
- NOT having the PCP present during the ICP
- Having the ICP be carried out by someone *other* than the PCP or a staff member dependent on the PCP
- Having an independent witness to the ICP

The PCP's demeanor alone can influence a patient's decision. Patients should choose to enter a study on its own merits because they understand the risks and benefits (not simply because they value and trust the PCP's judgment).

When an investigator is also a patient's PCP, the investigator must employ one or more of the options identified above during the consent process.

Conflicts of Interest

A conflict of interest is a situation in which financial or other personal considerations (significant interests) have the potential to compromise or bias professional judgment and objectivity. An apparent conflict of interest is one in which a reasonable person would think that the investigator's judgment is likely to be compromised. A potential conflict of interest involves a situation that may develop into an actual conflict of interest. Apparent and potential conflicts of interest can damage the trust and confidence that people have in research.

Goodwyn IRB requires an investigator to disclose significant interests held by him or herself, a research staff member, an immediate family member, or the research site business entity with any company that may benefit from proposed research activity. It is important to note that a conflict of interest exists whether or not decisions are affected by a personal interest; a conflict of interest implies only the potential for bias, not a likelihood. It is also important to note that a conflict of interest is not considered misconduct in research. However, failure to disclose significant interests is serious and could lead to suspension or termination of IRB approval.

Goodwyn IRB may elect to have a potential conflict of interest disclosed to potential subjects in the informed consent process/document. However, when the conflicting interest may adversely affect the research participants or the credibility of the research, Goodwyn IRB may require additional precautions and safeguards.

Vulnerable Subject Populations

Vulnerable populations are people who are at increased risk of potential exploitation. Their circumstances render them particularly sensitive to the perceived authority of the investigator, the hoped for benefits / risks of the study, the language being used to describe the study and its requirements and/or the anticipated compensation for participation. The IRB requires additional measures be taken in the consent and site processes (spanning the duration of the study) to ensure that these subjects clearly understand the study and that their decision to participate is not influenced by factors such as those mentioned above. Where appropriate, the IRB will consider the amount of experience that an investigator has with the vulnerable subjects and research. Vulnerable populations include the following:

- Children / Minors
- Adult Illiterate and Educationally Disadvantaged;
- Adult subjects who lack of decision-making capacity, requiring the use of Legally Authorized Representation (LAR);
- Pregnant women;
- Economically Disadvantaged;
- Prisoners;
- Physically Handicapped;
- Seriously Debilitated or Diseased individuals;
- Individuals afflicted with Life-Threatening conditions (e.g., HIV/AIDS, Hepatitis, advanced neoplastic disease);
- Site or Sponsor Employees;
- Non-English Speaking populations.

The additional measures required are detailed below:

Children/Minors

- Assent from minors over a certain age is required. Goodwyn IRB will determine the age over which assent will be required based on the study protocol.
- The minor will be given the opportunity to ask questions about the protocol without the presence of his/her parent/guardian.
- The minor will not be enrolled or maintained in the study unless s/he provides ongoing affirmative consent.
- The site must verify with local counsel state law requirements governing parental / legal guardian consent to research with children as well as circumstances in which the child's assent is required, those in which an adolescent may be able to give consent to participation him or herself, and those in which a guardian may give consent for a minor child. These requirements may vary depending upon the procedures and treatments involved in a research study.
- If an emancipated minor will be enrolled without parental permission, the study investigator must contact Goodwyn IRB prior to enrollment to obtain instructions regarding the consent process and appropriate safeguards.

Adult Illiterate and Educationally Disadvantaged Subjects

- A witness, independent of the study team, must be present during consent process. The investigator or members of the study staff are not considered independent witnesses.
- Prospective subjects falling into this category will be asked to indicate agreement with the consent process by marking the document in whatever way they wish to signify their intent to participate.
- The witness must also sign and date the consent, attesting to the completeness of the presentation, that the subject understood the information before the subject indicated (marked) his/her consent, and that the subject's consent was voluntary.

Subjects Who Lack Decision-Making Capacity

- The IRB will determine whether the use of a legally authorized representative (LAR) is appropriate under the protocol and whether the investigator's site appears qualified to use an LAR.
- The site must verify any state-law requirements on the use of LARs in research by consulting with local legal counsel.
- A determination of capacity must be made prior to the consent process and must be documented in the subject's source record. A general mental status assessment is not sufficient. Instead, investigators must present specific material relevant to the research project and evaluate the prospective subject's ability to understand and appreciate the information. For this purpose, Goodwyn IRB requires either of the following tools: 1) the consent document and "Suggested Tool for Assessment of Informed Consent" (attached), or 2) The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR).
- Prospective subjects / LARs must be given additional time to ask questions.
- Surrogate consent must be obtained from a LAR, however
- The prospective subject cannot participate in the study unless s/he provides ongoing affirmative assent.
- If research subjects include those in whom decision-making capacity might fluctuate, Goodwyn IRB will determine the appropriate consent process during review of the study protocol and inform study investigators about the required safeguards.

Pregnant Women

- All potential risks to both mother and fetus must be clearly explained at the point of obtaining written consent as well as throughout the on-going informed consent process.

Economically Disadvantaged Subjects

- Given the local economic standards, any compensation and other inducements must not be so great that a potential subject would consent against his/her own judgment. The IRB can assist in determining appropriate amounts of compensation if local standards are not readily available.
- All compensation must be pro-rated and all requests for payment prior to your designated payment intervals by subjects must be honored.

Prisoners

- The IRB reviewing the protocol must include an individual capable of representing prisoners' rights.
- Should a study subject become incarcerated at any point during the study, you must contact Goodwyn IRB immediately.

Sponsor / Site Employees (including their family members)

- Such prospective subjects may receive a broad invitation to participate, but must not be approached directly.

- The informed consent process must not be administered by an individual in a supervisory position over the prospective subject.

Non-English-speaking Subjects

- Language-specific translations of English language informed consent documents and study materials must be used. These translations can either be provided by the study sponsor or can be acquired through the IRB.
- All translated material requires certification of translation that must be confirmed via review by the IRB.
- Additionally, all sites that intend to draw from any Non-English speaking populations are required to have an individual available on premises to assist in a translational role when recruiting and attending to subjects in the native tongue of the participant.

Other Vulnerable Subjects

The inclusion of seriously debilitated or diseased individuals or individuals afflicted with life-threatening conditions (e.g., HIV/AIDS, Hepatitis, advanced neoplastic disease) is usually identified at the protocol level. The IRB determines appropriate measures during the review of the protocol and will communicate those measures to study investigators.

Physically handicapped and / or visually impaired individuals may need assistance with a variety of things associated with the protocol, e.g., opening study medication containers, easy access to all testing facilities, assistance with written instructions or diaries, etc. The investigator must provide for appropriate assistance.

Legally Authorized Representatives (LAR)

A legally authorized representative (LAR) is defined by 21 CFR § 50.3 as, "...an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." The IRB will determine whether the use of a LAR is appropriate under the protocol and whether the investigator's site appears qualified to use a LAR.

A properly qualified LAR may makes decisions on behalf of and for the subject, but the specifics of how to qualify an LAR are defined in state laws. Investigators must ensure compliance with his or her state's laws that govern LARs and to have a system in place to ensure that only properly qualified LARs consent to research decisions for a subject. Investigators must document the legal authority and relationship between the subject and the LAR in the subject's source record.

Privacy and Confidentiality

Privacy and confidentiality are not the same. Privacy refers to persons and their ability to control access of others to themselves. To respect privacy in research is to provide conditions acceptable to the research subject under which inquiries or interventions related to the research will take place. For biomedical research investigators must a private setting for all interactions related to the research.

Confidentiality refers to information and the agreements that are made about how access to an individual's information is protected (access by others is restricted). In research, individuals disclose information about themselves in a relationship of trust with the expectation that it will not be disclosed to others without their permission or in a way that is inconsistent with their original understanding (during the consent process). Investigators must protect confidential information. All information must be organized, stored and maintained in a manner that prevents access by anyone not authorized as described in the consent process (and document). The same level of security must be continued after the research is completed for as long as the records exist.

Breach of confidentiality occurs when confidential information is accessed or disclosed by unauthorized individuals. The mere fact that information might be disclosed does not mean that subjects will be seriously harmed; the critical question is whether the disclosure might be potentially damaging. The harms to subjects resulting from breach of confidentiality can include psychological, social and/or economic, and depend upon the nature and sensitivity of the research. A breach of confidentiality must be reported to the IRB as described below.

Reporting Responsibilities of Study Investigators

Unanticipated problems involving risks to participants and others (including unexpected and related adverse events) must be reported to Goodwyn IRB as soon as possible after the principal investigator learns of the event, but in all cases within 10 working days. Unanticipated problems involving risks to participants or others are defined as any incident, experience or outcome that meets **all** of the following criteria:

- Unforeseen (not expected by the researcher or the research participant) given the research procedures and the subject population being studied;
- Related or probably related to participation in the research or if the event or problem probably or definitely affects the safety, rights and welfare of current participants; **and**
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Events/problems that meet these criteria should be reported through the Adverse Event, Unanticipated Problem, Updates and Alerts and Protocol Deviation Report forms. These forms and instruction will be provided with your study approval and are also available at www.GoodwynIRB.com.

What needs to be reported?

- **Unanticipated problems involving risks to participants or others (see above definition) including but not limited to:**
 - Unexpected, related adverse events
 - A breach of confidentiality or privacy that involves real or potential risk such as unauthorized use or disclosure of protected health information (PHI)

- Unanticipated adverse device effects (*new information about the 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 of severity, or degree of incidence or any other unanticipated, serious problem associated with a device that relates to the rights, safety or welfare of subjects*)
- Unanticipated problems identified by sponsors and communicated to investigators in aggregated reports regarding adverse events.
- **New Information indicating a change to the risks or benefits of the research including but not limited to:**
 - Data and Safety Monitoring Board (DSMB) summary reports that indicate that frequency or magnitude of harms or benefits may be different from that initially presented to the IRB
 - Publication that shows that the risks or potential benefits of the research may be different from that initially presented to the IRB
- **Change in FDA labeling or withdrawal from marketing** of a drug, device, or biologic used in a research protocol
- **Incarceration** of a participant in a protocol not approved to enroll prisoners
- **Complaints** from participants or others involved in the research that indicate either unexpected risks or that cannot be resolved by the research team
- Site visit monitoring reports, all audits, inspections and subsequent reports including Department of Health and Human Services (DHHS), FDA, NIH, NCI, and cooperative groups that are conducted for specific cause
- Changes to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research subject, or a protocol deviation (an accidental and unintentional change or departure from the IRB approved protocol that placed one or more participants at risk, or has the potential to occur again)

Recruitment / Retention and Other Written Materials for Subjects

When an investigator intends to recruit subjects through physician referral, the referring physician must make the first approach to a prospective subject regarding the research study or must obtain permission from that individual to be contacted by the investigator.

When obtaining any health information about prospective subjects from referring physicians, investigators must ascertain that the referring physician has obtained authorization from the prospective subject for such sharing and make efforts to limit such information to the minimum necessary required for study purposes. For more information about HIPAA, please visit

www.GoodwynIRB.com/HIPAA1.htm.

An investigator may also conduct a review of his/her patients' files to identify prospective subjects for a research study. If the investigator's research site is a covered entity under the HIPAA Privacy Rule, the investigator's Notice of Privacy Practices must describe this potential use of a patient's record.

Recruiting activities are the beginning of the informed consent process. Consequently, the IRB requires prior review and approval of all recruitment materials that will be seen or heard by prospective participants, including any information about a research study that will be provided when contacting prospective subjects to set up an appointment. Likewise, participant retention programs intended to encourage enrolled participants to continue participation in a study must be reviewed and approved by the IRB before implementation.

The study sponsor may require pre-review and approval of your material. Check with the study sponsor before submitting material to Goodwyn IRB.

Reviewed materials that require modifications may be "provisionally approved." Provisionally approved materials must be resubmitted after making the requested modifications. The IRB will verify the incorporation of these modifications prior to issuing an approval letter. Audio visual ads should be submitted in final form after receiving IRB approval for the written script.

A participant retention program is a program that involves the provision of gifts or other incentives to enrolled participants to encourage their continued participation in a study. As an example, an investigator might offer \$20 gift cards to participants who reach a particular study visit milestone. Or, a sponsor might provide inexpensive gifts (e.g., tote bags, pens, t-shirts, mugs, etc.) throughout a study. Goodwyn IRB must review and approve the retention program plans prior to implementation.

Once the IRB has approved written subject materials, any changes to the content or presentation of those materials must be reviewed and approved prior to use.

Definitions:

Unexpected Adverse Event

An unexpected adverse event is any adverse event occurring in one or more subjects participating in a research protocol, whose nature, severity, or frequency is **not consistent** with, either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol related-documents, such as the IRB-approved research protocol, any applicable investigator brochure (IB), and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease or condition of the subject(s) experiencing the adverse event.

Related Adverse Event

It is the responsibility of the principal investigator to make the initial determination of a

relationship between an adverse event and any investigational agent(s), intervention, or research study procedure.

- An adverse event is “related to the research” if in the opinion of the principal investigator, it was more likely than not related to the investigational agent(s) or intervention.

Protocol Deviation

A Protocol Deviation is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol Deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research.

Protocol Deviations are unplanned and unintentional events. Any changes in the research protocol during the period, for which the IRB approval has already been given, may not be initiated without submission of an amendment for IRB review and approval.

The IRB recognizes that some protocol deviations pose no conceivable threat to participant safety or scientific integrity. As such, reporting is left to the discretion of the PI within the context of the guidelines below. Any report of a Protocol Deviation to the IRB should be made in a timely fashion but no later than within 10 days of its occurrence or identification.

Examples of Reportable Protocol Deviations

- Enrolling participants who do not fulfill inclusion/exclusion criteria
- Participant receiving any study related activity such as treatment, procedures, testing, or drug administration prior to obtaining documented IRB approved informed consent
- Adverse Event reporting procedures not followed
- Variations from protocol in the use of a study device from protocol
- Variations in drug dosing/dispensing/storage requirements
- Use of Prohibited medications
- Incorrectly performed or missing protocol-required tests and procedures
- Incorrect handling of biological samples
- Premature “unblinding” of research treatment or data
- Loss or corruption of study data
- Protocol Deviations identified by sponsor monitor visits, or study coordinator that may affect the safety of a participant or the integrity of study data

Examples of Non-reportable Deviations

- Withdrawal of participant for logistical reasons (e.g. moved out of town)
- Minor variation in clinic visits/follow-up (e.g. “Day 20 Visit” on day 24) if no protocol medication, treatment, or supervision is missed



We Would Like To Hear From You

Please contact Goodwyn IRB to obtain answers to questions, express concerns, and convey suggestions regarding our Human Research Protection Program.

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