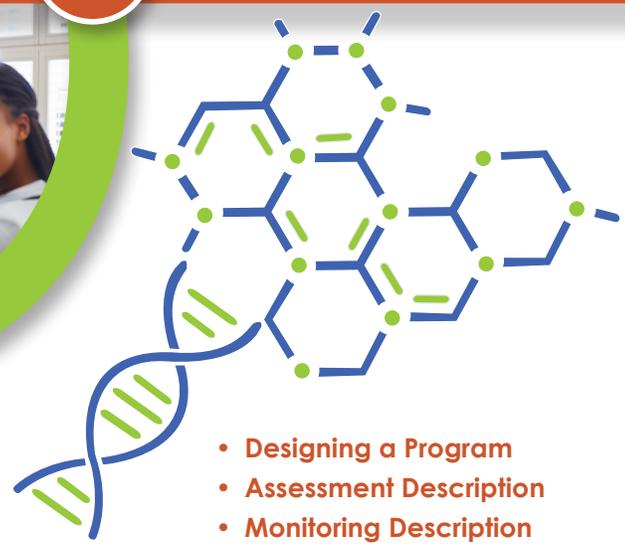


National Institute of Mental Health

Human Subjects Research Protections Toolkit



Developing **SECTION 1** Protections



- Designing a Program
- Assessment Description
- Monitoring Description



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Introduction

A human research protection program (HRPP), in part, aims to protect human research subjects. The National Institute of Mental Health (NIMH) protects potentially vulnerable **SUBJECTS** with **ADVOCATES** who support the individual subject as well as educate and advise **RESEARCHERS**.

This NIMH Toolkit for Human Subjects Research Protections is based on the NIMH's experience conducting research with potentially vulnerable subjects. Our aim is to help research organizations assess, implement, and refine appropriate levels of human subjects protections during all phases of research (submission of the initial protocol to the Institutional Review Board [IRB] through subject transition out of the protocol). Research organizations need to tailor these practices to suit their own standards and legal and policy requirements.



SUBJECTS

ADVOCATES

RESEARCHERS

Section 1: Developing Protections introduces the NIMH Human Subjects Protection Unit (HSPU) program. Primarily, it describes the elements of a protections program and how to assess which elements a research organization might incorporate.

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Disclaimer: This NIMH Toolkit does not incorporate state or local law or organizational policies, nor does it address possible applicable federal law or speak to regulatory interpretation of 45 C.F.R. § 46. It does not address specifics for a particular type of protocol or IRB requirements. This Toolkit is the opinion of the NIMH intramural program and is subject to change.



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Background: Toolkit History and Frame of Reference



1.1

History

The National Institute of Mental Health (NIMH), an institute within the National Institutes of Health (NIH), a component of the U.S. Department of Health and Human Services, is comprised of an extramural and an intramural program. The extramural program provides grants and educational services to research programs and community agencies around the country and worldwide. The intramural program conducts basic and human subjects research relating to a broad spectrum of mental health disorders at the NIH Clinical Center (CC) in Bethesda, MD.

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Human subjects protections sometimes develop in response to past abuses (e.g., Nazi experiments, Tuskegee Syphilis study). In 1998, the National Bioethics Advisory Commission (NBAC) published *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*. NBAC recommendations included that Institutional Review Boards (IRBs) should require independent, qualified professionals to assess a potential subject's capacity to consent for some greater than minimal risk studies.*

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.†

NIMH took the lead and proactively created a program to enhance human subjects protections for potential subjects and subjects participating in NIMH protocols.

- In July 1999, the NIMH Office of the Clinical Director established an independent monitoring group to operate at the NIH CC. Initially named the Centralized Office for Recruitment and Evaluation (CORE), the impetus for the creation of the CORE was the belief that “respect for persons incorporates at least two ethical convictions; first, individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.”‡ The CORE aspired to improve protections for research subjects during all phases of research.

*National Bioethics Advisory Commission (NBAC). *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity: Report and Recommendations of the National Bioethics Advisory Commission*. Rockville, MD: NBAC, 1998, Vol. 1.

†Criteria for IRB Approval of Research, 45 C.F.R. § 46.111 (b), 2018.

‡National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, Bethesda, MD: U.S. Govt. Print. Off., 1978, Part B: Basic Ethical Principles, Section 1. Respect for Persons.



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Background: Toolkit History and Frame of Reference



1.2

- In 2007, the CORE was re-named the Human Subjects Protection Unit (HSPU) and its clinicians titled Clinical Research Advocates (CRAs). The dual focus of recruitment and subjects protection was redirected to implement a more comprehensive oversight of human subjects protections.
- The HSPU program continues to evolve, as does the definition of potentially vulnerable populations and recommendations for their protection.

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The NIMH Toolkit is based on the HSPU's experience and best practices. It is available at no cost to the public and to research organizations aspiring to define their own human subjects protections programs.

Frame of reference

When designing a human subjects protections program, it is important to take into consideration the following NIMH Toolkit frame of reference:

- The NIMH Toolkit uses the term subject to refer to those people enrolling or enrolled in research. The term was chosen to match federal regulation language. The term patient is not used to avoid therapeutic misconception. In practice, the preferred term is participant or volunteer.
- A subject population identified as potentially vulnerable (e.g., subjects diagnosed with a mental disorder) does not, in and of itself, identify all individuals within that population as vulnerable. Similarly, not being identified as part of a potentially vulnerable population does not provide immunity to becoming vulnerable. Situational context (e.g., subjects who are employees, relatives of the researcher, or who have a medical condition) may impact vulnerability.
- The NIH CC is a research-based hospital and every person seen in the clinics or inpatient units is enrolled in a protocol.
- The HSPU is a program within the NIMH that implements enhanced human subjects protections for potentially vulnerable subjects as part of a larger NIMH intramural human research protection program (HRPP). A complete HRPP may also include safety and compliance oversight (e.g., data safety monitoring board or independent safety monitor).
- Subject monitoring at the HSPU level is with an individual subject in real-time, as opposed to subject monitoring as part of a protocol safety plan that reviews groups of subject data at specific points in time over the course of the research.



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Background: **Toolkit History and Frame of Reference**



- The NIMH allocates resources to maintain the HSPU. Outside organizations may take portions of this NIMH Toolkit and implement them in a manner suitable to their structure and resources (e.g., through a bioethics department or other independent group).
- At the NIH CC, documentation takes place in the medical record. Outside research organizations should follow their own documentation policies and procedures.
- This NIMH Toolkit does not interpret federal policy. References to 45 C.F.R. § 46 are footnoted for the reader's convenience.

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Background: The NIMH HSPU Program



1.4

The HSPU program

The HSPU functions under the auspices of the NIMH Office of the Clinical Director whose authority and support are crucial for the implementation of the program. The HSPU protects potentially vulnerable subjects participating in NIMH intramural research. The HSPU advises researchers in assessing, developing, and implementing appropriate levels of human subjects protections during all phases of research, from protocol development through a subject's completion of a protocol.

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The HSPU is comprised of NIMH CRAs who report directly to the Clinical Director, are not engaged in clinical research recruitment, and are not researchers. This approach eliminates any undue pressure and assures independence from the researchers. If the researcher and the advocate are in conflict, the NIMH Clinical Director serves as arbiter.

Additionally, the HSPU joined with the NIH CC Bioethics Department to form the Ability to Consent Assessment Team (ACAT) to provide assessments and consultation throughout the NIH CC.

The HSPU functions

The following HSPU functions are essential both for the protection of potential subjects and subjects and to the integrity of the protocols in which they are enrolled.

- **Human subjects protections**

The HSPU assures protection of and support to potentially vulnerable subjects participating in research. Assessment and monitoring activities are

- Capacity assessment
- Ability to assign a surrogate decision-maker assessment
- Surrogate decision-maker assessment
- Consent monitoring
- Subject monitoring

- **Consultation**

As a non-voting consultant, the HSPU reviews protocols and makes recommendations for improving human subjects protections to the NIH Institutional Review Board (IRB). Additionally, the HSPU interprets and assists in the application of federal, NIH, and NIMH human subjects research regulations and policies.



Background: The NIMH HSPU Program



- **Researcher education and training**

The HSPU provides human subjects protections education and training throughout the NIH, to outside organizations, and at national meetings. The local IRB requires all researchers obtaining informed consent to complete the HSPU's Elements of a Successful Informed Consent training. This training includes how to obtain consent, the elements of the informed consent process, and relevant federal and organizational policies.

Additionally, the HSPU administers an *Objective Structured Clinical Examination (OSCE) for the Evaluation of the Informed Consent Process* (see Toolkit Section 2) to evaluate the ability of researchers to obtain informed consent.

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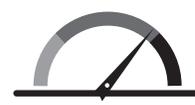
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Designing a Program: **Developing a Program**

If any one of the following situations exists, developing a program with specific tools to enhance human subjects protections may be helpful.

<p>Researchers will enroll potentially VULNERABLE POPULATIONS as subjects</p> 	<p>Anticipated protocol is MORE THAN MINIMAL RISK and there is NO PROSPECT OF DIRECT BENEFIT</p> 	<p>Anticipated research is CONTROVERSIAL</p> 
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Enhanced protections plans may be initiated by

<p>RESEARCHER request</p> 	<p>Organizational POLICY decision</p> 	<p>IRB requirement</p> 
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Designing a Program: **Costs and Considerations**



1.7

A human subjects protection program should have advocates and logistical and administrative support.

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Advocates

Advocates are a primary component of a human subjects protections program. The number of advocates required for a program depends on the number of protocols and level of advocate involvement. Most of the advocate's time is spent monitoring, assessing, and supporting subjects; attending interdisciplinary rounds; consulting with interdisciplinary research teams; and documenting. The advocate's remaining time is spent training researchers and consulting with the IRB. The advocate's schedule includes time for both planned and unexpected consults. Coverage plans are made for advocate absences.

Workspace

Ideally, each advocate has an individual desk, computer, and telephone, as well as access to a private space for consultation and discussion.

Legal support

Advocates need access to legal counsel. Laws vary from state to state and may change over time. Legal counsel may review and clarify a potential subject's legal documents. For example

- Custody arrangements (i.e., which parent(s) is authorized to consent for a minor)
- Legal guardianship of an adult (i.e., whether a legal guardian is authorized to give consent for a potential subject to participate in a specific protocol and under what circumstances)

Quality assurance

A human subjects protections program should be reviewed periodically with feedback from organizational leadership, researchers, the IRB, and subjects.

Ongoing training

Advocates should

- Maintain professional licenses
- Stay current on research ethics, federal regulations, and human research subjects protections issues



Designing a Program: **Advocate Qualifications**



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A human subjects protections program is based on advocates having both a clinical and an ethics background.

Clinical training

Advocates are masters prepared clinicians (e.g., social workers, psychologists, or nurses). Questions and situations that arise as part of their work can be complicated and nuanced. Advocates require strong clinical understanding, knowledge of systems, critical thinking, flexibility, and the ability to negotiate conflict.

Experience

Experience in both clinical and research settings allows advocates to understand the complex nature of subject enrollment and to provide support and education. The ability to observe and assess the subtleties of human interactions and non-verbal communications, as well as the ability to provide support, is required.

Bioethics training

Knowledge and training in the ethical principles underpinning human subjects protections are essential to the application and monitoring of ethical research practices by advocates.

Independent of the research

Advocates must be independent of the research (i.e., are not researchers on the protocol; do not report to, nor are supervised by, the researcher; and are not obligated in any way to influence recruitment or retention of subjects). The independence of advocates allows for neutrality when assessing and monitoring a subject.



Assessment Description: **Capacity Assessment**



1.9

Determines the potential subject's or subject's ability to provide consent to research participation

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A capacity assessment is an evaluation by a trained advocate of an adult potential subject's ability to provide informed consent for a specific protocol at a specific time. The researcher educates the potential subject about the protocol prior to the advocate administering the capacity assessment. The advocate documents the assessment outcome according to organizational policy.

The terms capacity and competence are often misunderstood and used incorrectly. The terms are not interchangeable.

- Capacity is an assessment, determined by a clinician, of a potential subject's ability to understand and make decisions about participating in a specific protocol at a specific time. It is not related to a potential subject's abilities and rights outside of the research setting.
- Competency is a legal status often determined by a court of law. It is a broader determination than capacity.

Potential subjects determined not to have consent capacity will fall into one of two categories:

- Those who previously had the ability to provide informed consent but at the time of assessment no longer have that ability
- Those who have never had the ability to provide informed consent

Additional points to consider

- Consent capacity may fluctuate during research participation and may be influenced by factors such as medication or worsening symptoms.
- Capacity assessments are generally designed to assess capacity at time of initial consent but can be adapted for assessment of consent capacity during protocol participation.
- The potential subject can be found to have consent capacity for a minimal risk protocol but not for a more than minimal risk protocol.

Capacity assessments generally assess four domains: understanding, appreciation, reasoning, and choice. It is useful to have two types of capacity assessments (see Toolkit Section 2):

- A protocol-specific capacity assessment is used when a protocol requires some or all potential subjects be formally assessed prior to consenting. It is created in advance of anticipated potential subjects enrolling. To create the tool, the advocate incorporates specific protocol information including the diagnosis or illness being studied, the protocol procedures, and anticipated risks and benefits.



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Assessment Description: **Capacity Assessment**



- A generic capacity assessment is a basic assessment format that can be adapted when an unanticipated need for an assessment arises. To adapt the tool, the advocate incorporates specific protocol information including the diagnosis or illness being studied, the protocol procedures, and anticipated risks and benefits.

The tools should be created prior to administering the assessment.

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Assessment Description: **Ability to Assign a Surrogate Decision-Maker Assessment**



1.11

Evaluates the ability of an adult potential subject to choose a surrogate to make decisions on behalf of a potential subject or subject

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Although the potential subject may not have consent capacity, the potential subject may be able to identify a trusted person to help make decisions about healthcare and research participation. When the protocol allows for surrogate decision-maker consent and there is no other surrogate decision-maker identified, the advocate assesses the potential subject's ability to identify a surrogate decision-maker for healthcare decisions in research (see Toolkit Section 2, *Ability to Assign a Surrogate Decision-Maker Assessment*). The advocate documents the assessment outcome according to organizational policy.

If the potential subject is able to and does assign a surrogate decision-maker, this assessment is followed by the *Surrogate Decision-Maker Assessment* (see Toolkit Section 2). A potential subject who has consent capacity is considered able to assign a surrogate decision-maker and does not need a formal assessment to do so.

Background

The surrogate decision-maker (also referred to as substitute decision-maker, surrogate, legally authorized representative [LAR]* or proxy) may be a(n)

- Legal guardian
- Agent named in an advance directive (AD) such as a durable power of attorney (DPA) for health care or a living will
- Next-of-kin (NOK)

State law and organizational consent policies usually dictate when a surrogate decision-maker may be used for research. For example, a policy could state NOK may not be used except in limited circumstances (see Toolkit Section 4, NIMH Consent Process Flowchart).

There are two categories of surrogate decision-makers:

- Those whose status is in effect. This status applies to legal guardians who are appointed by a court of law. The legal guardian can provide consent for the potential subject. The potential subject may provide only assent because the potential subject does not have legal competency.
- Those whose status is in effect only in specific circumstances. This status could exist with a surrogate decision-maker assigned through an AD, DPA, living will, or NOK policy. It is invoked only when the potential subject loses consent capacity.

When the potential subject has a pre-existing surrogate decision-maker, the advocate may consult with legal counsel regarding any limitations to research participation (e.g., DPAs may cover only financial decisions or a state may allow surrogate consent only for research that has a prospect of direct benefit).

*Definitions for Purposes of this Policy, 45 C.F.R. § 46.102 (7) (ii) (i), 2018.



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Assessment Description: **Surrogate Decision-Maker Assessment**



Evaluates the surrogate decision-maker's ability to provide consent and, ideally, to represent the subject's wishes

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The Surrogate Decision-Maker Assessment (see Toolkit Section 2) evaluates the appropriateness of a person to serve as the potential subject's surrogate decision-maker. If the potential subject is found not to have consent capacity, the surrogate decision-maker may provide consent on behalf of the potential subject. This assessment is not a capacity assessment of the surrogate decision-maker.

Once a surrogate decision-maker is identified and before research moves forward, the appropriateness of the surrogate decision-maker is assessed by the advocate. This assessment may include whether the surrogate decision-maker understands the difference between research and clinical care and the risks and potential benefits of each. The surrogate decision-maker should understand the essential elements of the protocol as explained in the informed consent document. Ideally, the surrogate decision-maker should understand the potential subject's values, preferences, and choices regarding research participation.

Advocates, researchers, and organizations should consider whether participation will proceed if a surrogate decision-maker is found to be appropriate, but the potential subject does not want to participate in the protocol.

The advocate documents the assessment outcome according to organizational policy.



Monitoring Description: **Consent Monitoring**



Assures the elements of the protocol consent are discussed by a researcher and a potential subject

The advocate is present during the consent discussion between the researcher and the potential subject or the surrogate decision-maker and assures the required elements of the protocol consent are discussed (see Toolkit Section 2, Consent Monitoring Checklist). The advocate monitors the quality of the conversation to assure information is accurate, descriptions are clear, and any questions or concerns raised by the potential subject or the surrogate decision-maker are answered and clarified. The advocate witnesses the consent process and documents according to organizational policy.* This standard may change with the facts of a situation (e.g., the purpose and requirements of a witness if a short form consent is used†). A signed copy of the consent form is given to the person(s) providing consent.‡

There can be a need to obtain telephone consent. For example, the protocol requires consent from both parents, but only one can be present at the time of the consent process. The IRB must approve the telephone consent process in advance.

Prior to the telephone conversation, the advocate assures the party participating off-site has a copy of the consent form. The advocate is present with the researcher at the time of the call to monitor the elements of consent.

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*The advocate may sign as the witness. Check your organizational policy for any specific requirements.

†Documentation of Informed Consent, 45 C.F.R. § 46.117 (b) (2), 2018 requires a witness to the oral presentation.

‡Documentation of Informed Consent, 45 C.F.R. § 46.117 (a), 2018.



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Monitoring Description: **Assent Monitoring**



1.14

Assures the quality of the assent discussion for adults without decision-making capacity and minors by verifying the agreement of the potential subject to participate in research

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The assent discussion is a less complex review of a consent and may take place at the same time as consent. Advocates need to know if assent is required for a protocol per IRB determination.* The advocate is present for the assent discussion between the researcher and the minor potential subject or the adult potential subject who lacks consent capacity. While the parent(s) or surrogate decision-maker participates in the full consent discussion, the researcher's assent discussion with the potential subject focuses on that person's decision to participate in the protocol.

The assent process includes monitoring for subject dissent. Failure of the potential subject to object to participation in the protocol should not be construed as assent.† There may be situations in which assent is not required (e.g., in a pediatric protocol with a prospect of direct benefit that is important to the health or well-being of the potential subject and is available only in the context of the research).

Dissent may be expressed behaviorally—for example, through body language, lack of engagement in the assent process, or refusal of procedures after research begins. Depending on how a protocol is written, it may be possible for a potential subject to decline to participate in some procedures while participating in others.

Advocates, researchers, and research organizations need to know applicable state law regarding the age of consent. Researchers should anticipate and plan for continued enrollment if subjects do not have consent capacity when they reach the age of majority.

The advocate documents the assent discussion according to organizational policy.

*Requirements for Permission by Parents or Guardians and for Assent by Children, 45 C.F.R. § 46.408, 2018.

†Definitions, 45 C.F.R. § 46.402 (b), 2018.



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Monitoring Description: **Subject Monitoring**



1.15

Assures ongoing consent during inpatient or longer-term protocol participation

Subject monitoring is with an individual subject in real-time, as opposed to subject monitoring as part of a protocol safety plan that reviews groups of subject data at specific points in time over the course of the research or that requires prompt reporting of certain medical or other problems.

To verify ongoing informed consent, the advocate regularly visits subjects over the course of their participation to assess current wishes, understanding, questions, and concerns regarding continued participation in the protocol.

The advocate monitors the ongoing informed consent of subjects during face-to-face conversations (see Toolkit Section 2, *Subject Monitoring Guide*). Additionally, the advocate reviews the medical record and participates in interdisciplinary meetings with the research and clinical staff. The advocate encourages the subject to communicate questions and concerns to the researcher. If needed, the advocate acts as the subject's voice to bring concerns to the attention of the researcher. The advocate facilitates the resolution of issues to assure the subject's wishes regarding research participation are respected.

The advocate documents these discussions according to organizational policy.

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