

MODULE TWO: The Role of the Institutional Review Board

Module two reviews the role of the institutional review board in the protection of the human participants in research, focusing on the federal regulations governing research activity. Further discussion of investigator responsibilities are found in Module 3 (research integrity and conflict of interest) and Module 4 (proper conduct of clinical trials). The Children's Hospital Philadelphia (CHOP) Institutional Review Board functions under a [Multiple Project Assurance](#) negotiated with the federal [Office for Human Research Protections \(OHRP\)](#), which requires that all research performed at CHOP be reviewed according to a uniform standard. That standard is found in [45 CFR 46](#) (a.k.a. "The Common Rule"). In addition, research involving drugs, devices, and biologics may be subject to [FDA regulations found in 21 CFR 50 and 56](#). These regulations are consistent with respect to basic IRB protections and informed consent. However, the FDA has no regulations that are specific to children such as that found in [Subpart D of 45 CFR 46](#). Nevertheless, CHOP applies the additional protections for children as research participants found in Subpart D to all research reviewed at CHOP. It is impossible in this training program to address all of the pertinent regulations that may apply to a given research project. If a specific question is not addressed upon reviewing the available regulations and guidance available on the Internet, the investigator should call the [Office of Research Regulatory Affairs](#) at 215-590-2830 for specific advice.

Any research activity involving human subjects that is conducted by a CHOP investigator or employee, regardless of location, is subject to review and approval by the CHOP IRB. In addition, any research activity involving human subjects that occurs within a CHOP facility, regardless of who performs it, is subject to review and approval by the CHOP IRB. The first question then is whether or not an activity constitutes research with human subjects. Research is defined as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (45 CFR 46.102d). A human subject is defined as "a living individual about whom an investigator conducting research obtains [either] data through intervention or interaction with the individual, or identifiable private information" (45 CFR 46.102f). At times, it may be difficult to determine whether any given activity constitutes research. If an investigator interacts with an individual, or collects data about that individual, for other than the sole purpose of providing clinical care, that activity may constitute research and should be discussed with the IRB office. Also, the evaluation component of an existing demonstration and/or service program may include research activities that should be reviewed by the IRB. When in doubt, ask.

The regulations specify a number of research activities that are considered exempt from IRB review (45 CFR 46.101b). However, CHOP policy states that only the IRB can determine whether a specific research activity is exempt, based on a written request from the investigator. Exempt research activities include: (1) research conducted in established or commonly accepted educational settings, involving normal educational practices; (2) research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects; and (3) some research and demonstration projects which are designed to evaluate public benefit or service programs.

For example, the review of medical records would be considered exempt if the investigator was not able to link the data collection sheet with the specific medical record once data collection was completed. As most investigators want to be able to return to the specific medical record to verify data, a simple

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inclusion of a case number linked to a medical record number renders the research ineligible for exemption. In addition, to be considered exempt, all of the data, documents or specimens need to exist at the start of the study. Any prospective collection of data, documents or specimens would disqualify the study for exemption. There is an additional category of exempt research which involves the use of educational tests, survey procedures, interview procedures or observation of public behavior, provided that the research does not place the subjects at risk of criminal or civil liability or other personal injury. This category, however, does not apply to research involving children (45 CFR 46.401b). The determination that certain research activities are exempt from IRB review can only be made by the IRB upon written request by the investigator. If exempt, the research is not subject to continuing IRB review, provided that there is no change in the research.

There are also some categories of research that may be reviewed by the IRB using an expedited review procedure. Expedited review means that the review can be performed either by the IRB chairperson and/or designee who may either approve the research or refer it to the full IRB (45 CFR 46.110b). Other than the number of copies required, there is no difference between expedited and full IRB review with respect to the IRB protocol application required of the investigator (such as the face sheet, narrative summary, informed consent form, other pertinent forms such as biological specimens or genetic testing, the full grant application or sponsor protocol, and the investigator brochure). For research to be considered expedited, it must meet both of two conditions. First, it must present no more than minimal risk to human subjects. Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102i). Second, it must fit into one of the [identified research categories](#) that are eligible for expedited review, as established by the Secretary of HHS. These categories include: limited clinical studies of approved drugs and/or medical devices; limited collection of blood samples; noninvasive prospective collection of biological specimens; collection of data through noninvasive procedures routinely employed in clinical practice (excluding general anesthesia, sedation, x-rays or microwaves); research involving data, documents, records or specimens that have been or will be collected solely for nonresearch purposes; collection of data from voice, video, digital or image recordings; and research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation or quality assurance methodologies.

For prospective blood collection using children to be considered expedited, the amount drawn may not exceed the lesser of 50 mL or 3 mL per kilogram in an eight-week period and collection may not occur more frequently than two times per week. Larger amounts of blood may be permitted by the IRB; however, such research would need to be reviewed and approved by the full IRB. It is expected that medical record research, or research involving laboratory testing of biological specimens, can be reviewed and approved using expedited IRB procedures unless the information being recorded or developed presents greater than minimal risk. Other than the amount of blood specified, there is no difference in the application of expedited IRB procedures between research involving adults and research involving children. All decisions that are made by expedited review are reported to and endorsed by the full IRB at the next appropriate meeting.

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The federal regulations specify specific criteria that an IRB must use in reviewing and approving research (45 CFR 46.111). Whether or not the IRB uses an expedited or full review process, the research must satisfy the following requirements:

- the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed for diagnostic or treatment purposes;
- risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;
- selection of subjects is equitable;
- when appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of subjects; and,
- when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

There are additional requirements that the research must satisfy if it involves, for example, prisoners ([45 CFR 46, Subpart C](#)) or children ([45 CFR 46, Subpart D](#)). If the research involves "any individual involuntarily confined or detained" (45 CFR 46.303c), the research may be subject to the additional protections defined in Subpart C. The investigator should contact the IRB office to discuss these specific requirements. In general, if children are involved, research that does not offer the prospect of direct benefit is restricted either to minimal risk research (45 CFR 46.404), or to research that involves only a minor increase over minimal risk, provided that (a) the intervention or procedure presents experiences to the child that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychologic, social, or educational situations; and (b) the intervention or procedure is likely to yield generalizable knowledge about the child's disorder or condition which is of vital importance for the understanding or amelioration of the child's disorder or condition (45 CFR 46.406) .

Research which offers the prospect of direct benefit to the individual child may involve greater than minimal risk, provided that the risk is justified by the anticipated benefit to the child, and the relation of the anticipated benefit to the risk is at least as favorable to the child as that presented by available alternative approaches (45 CFR 46.405). If research involving children cannot be approved by the IRB under one of these three categories, it can be referred to the Secretary of HHS for a determination of whether the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children, and will be conducted in accordance with sound ethical principles (45 CFR 46.407). The IRB must make all of these determinations based on the information provided by the investigator in the narrative summary of the protocol. In addition, the IRB must judge the qualifications of the investigator, and review any data collection forms, interview scripts, surveys or questionnaires. It is absolutely essential that the investigator provide the necessary information for the IRB to make the above determinations. The most common reason for either deferral or rejection of a protocol is the lack of information concerning one or more of the above requirements.

The final two requirements for IRB approval are that informed consent will be sought and appropriately documented, unless the IRB allows for a modification or

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waiver of either informed consent or documentation of informed consent. The federal regulations provide much detail about the specific elements that are required for informed consent (45 CFR 46.116). This, combined with the attention that IRBs often spend on the review and editing of informed consent documents, leads to the misimpression that informed consent is either the document or the moment in time when that document is signed. Informed consent should be considered a process of dialogue between the investigator and research participant that begins before, continues during, and persists after the research. The document does not replace, and should be seen as an adjunct to, this dialogue. This dialogue should take place under circumstances that provide the prospective subject sufficient opportunity to consider participation, minimizes the possibility of coercion or undue influence, and in language that is understandable (45 CFR 46.116). In addition, the informed consent document (and verbal consent if written documentation is waived) needs to include certain required elements. These required elements include:

- a statement that the study involves research;
- an explanation of the purposes of research;
- the expected duration of the subject's participation;
- a description of the procedures to be followed and identification of any procedures which are experimental;
- a description of any reasonably foreseeable risks or discomforts to the subject;
- a description of any benefits to the subject or to others which may reasonably be expected from the research;
- a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- for research involving more than minimal risk, an explanation as to whether any compensation and 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;
- an explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject; and,
- a statement that participation is voluntary, and that refusal to participate or a decision to withdraw from the study would not jeopardize the subject's relationship with CHOP or his or her medical care.

There are some additional elements of informed consent that should be included, when appropriate (45 CFR 46.116):

- a pregnancy statement involving possible risks to the fetus and prevention of pregnancy;
- circumstances under which the subject participation may be terminated by the investigator;
- any additional costs to the subject that may result from participation in the research;
- any consequences of the subject decision to withdraw if the withdrawal may involve risks that require an orderly termination of participation;
- a statement about sharing significant new findings that may relate to the subject's willingness to continue participation; and
- the approximate number of subjects involved in the study.

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The consent form needs to be signed by the subject or by the subject's legally authorized representative, and a copy given to the person who signed the form (45 CFR 46.117a). Further instructions about drafting an informed consent document can be found on the [Stokes Intranet](#). The CHOP IRB is in the process of developing an informed consent template that will suggest standardized language for many of the required elements and further assist in the development of an informed consent document. All of the requirements for informed consent also apply to parental permission (45 CFR 46.408).

There are certain conditions under which the IRB may approve a consent or permission procedure which alters or omits one or all of the required elements, or waive the requirement for informed consent altogether. The research must involve no more than minimal risk, the waiver or alteration will not adversely affect the rights and welfare of the subjects, the research could not practicably be carried out without the waiver or alteration, and, whenever appropriate, the subject will be provided with additional pertinent information after participation (45 CFR 46.116d). Generally, research involving existing data, documents or specimens may qualify for a waiver of informed consent, provided that the research will not result in any information that should be shared with the subject. In addition, parental permission can be waived if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children). An appropriate mechanism for protecting the children who will participate as subjects in the research needs to be provided, and the waiver may not be inconsistent with federal, state, or local law (45 CFR 46.408e). Generally, certain studies of adolescent behavior (such as contraception and/or sexual activity) may qualify for such a waiver. Finally, an IRB may modify or waive written documentation of informed consent. The regulations allow for the use of a modified "short form written consent document" combined with an oral presentation of the required elements provided that, among other requirements, there is a witness to the oral presentation, and the oral presentation follows an IRB approved script (45 CFR 46.117b). Written documentation of informed consent can be waived entirely if (1) the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; or (2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (45 CFR 46.117c). Examples where the written consent form may present a risk of confidentiality include data collection from individuals who are HIV-positive, or observational and interview research with individuals engaged in illegal behavior. Investigators who anticipate performing this type of research can obtain a [Certificate of Confidentiality](#) from the Department of HHS, which provides additional protections to the data from legal subpoena. Examples of minimal risk research which involve procedures that do not normally require written consent may include survey or questionnaire research, participant observation or interviews. It is important to remember that the waiver of written documentation does not absolve the investigator of the responsibility to obtain informed consent.

Although Subpart D requires that "adequate provisions are made for soliciting the assent of the children," there is no stipulation of any required elements for assent other than the fact that assent "means the child's affirmative agreement to participate in research." Furthermore, "mere failure to object should not, absent affirmative agreement, be construed as assent" (45 CFR 46.402b). The requirement for assent can be waived either if "the capability of some or all of the children is so limited that they cannot reasonably be

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consulted" or "the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research" (45 CFR 46.408a). This latter determination should be made at the time of initial IRB review, and reflects the parental role in making decisions concerning the child's health or well-being. Unless the assent of the child is specifically waived by the IRB either due to limited capacity or potential benefit unavailable outside of the research, the dissent of a child to either initial or continued research participation must be respected. Although many IRBs require separate assent forms for children, the current CHOP IRB policy is to allow for an oral presentation and then documentation by the investigator that assent was obtained.

In addition to the initial review and approval of a protocol and consent form, all modifications in existing approved protocols must be reviewed by the IRB prior to implementation unless necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103b4 and 109a). Minor changes in previously approved research may be approved using expedited review procedures (45 CFR 46.110b). The investigator is responsible for promptly reporting to the IRB "any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with the requirements or determinations of the IRB" (45 CFR 46.103b5). The IRB is also responsible for conducting continuing review of research appropriate to the degree of risk, but not less than once per year (45 CFR 46.109e). The continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including:

- the number of subjects accrued;
- a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research;
- a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and
- a copy of the current informed consent document.

Continuing review can be conducted by the IRB using expedited review procedures if the research qualifies for expedited review (as discussed above), or, for research which does not initially qualify for expedited review, expedited procedures may be used if the research remains open for follow-up or data analysis only, or no subjects have been enrolled and no new risks identified since the last continuing review. In addition, the IRB may determine at the initial review that the research presents no more than minimal risk and can be subsequently reviewed using expedited procedures, assuming that no additional risks have been identified. Finally, the IRB has the authority to observe, or have a third party observe, the consent process and/or research (45 CFR 46.109e).

Investigators participating in FDA-regulated clinical research involving drugs, biologicals and/or devices should be familiar with the applicable regulations. Although the FDA regulations on informed consent ([21 CFR 50](#)) and institutional review boards ([21 CFR 56](#)) are similar to 45 CFR 46, there are specific regulations pertaining to investigational new drug applications ([21 CFR 312](#)), investigational device exemptions ([21 CFR 812](#)), biological products ([21 CFR 312](#) and [600](#)), and financial disclosure for investigators ([21 CFR 54](#)). Although it is impossible to cover all the regulations in this module, there are several

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important points worth emphasizing. The FDA has published a number of Information Sheets that provide guidance for IRBs and clinical investigators on a number of issues, and is available on the Internet ([INFORMATION SHEETS -- Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update](#)). First, although the FDA does not regulate the "off label" medical use of otherwise approved drugs, devices and/or biologics, the use of an approved drug or biologic in a clinical investigation (21 CFR 312.3b) may require an [Investigational New Drug application](#) (IND) or [Investigational Device Exemption](#) (IDE) if the study involves "a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks)" (21 CFR 312.2b1). Second, the FDA requires submission of an IDE application for only [significant risk devices](#). A significant risk device presents a potential for serious risk to the health, safety, or welfare of the subject and is either (1) implanted, (2) used in supporting or sustaining human life, (3) of substantial importance in diagnosing, curing, mitigating or treating disease or otherwise prevents impairment of human health, or (4) otherwise presents serious risk to the health, safety, and welfare of the subject (21 CFR 812.3m). Third, the FDA allows for the [emergency use of an investigational biologic, drug or device](#) without prior IRB approval, provided that the patient is in a life-threatening situation, no standard acceptable treatment is available, and there is insufficient time to obtain IRB approval (21 CFR 561.02d). The FDA requires notification to the IRB within five working days or in accord with institutional policy (21 CFR 56.104C). It has been the policy at CHOP for the IRB to concur with the emergency waiver of prior IRB approval before the use of the investigational drug or device. Finally, investigators participating in industry-sponsored research usually must certify that they will conduct the research in accord with ["good clinical practice" - an international standard developed by the International Conference on Harmonization](#) for the conduct of clinical research. This standard will provide the framework for discussing investigator responsibilities in conducting clinical research in Module four.

Investigators are encouraged to consult with the Office for Research Regulatory Affairs prior to submitting a protocol, especially if the research design and/or consent process may vary depending upon the interpretation and application of the relevant regulations.