
Yale University Institutional Review Boards

IRB Policy 100 Institutional Review Board (IRB) Review of Human Subject Research Protocols or FDA- Regulated Activities Involving Human Participants

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Policy Sections	5
100.1 Projects Not Meeting the University, Department of Health & Human Services (DHHS) Office of Human Research Protection (OHRP) or Food & Drug Administration (FDA) Regulatory Definition of Research Involving Human Subjects	5
100.2 Research Subject to IRB Review	5
100.3 Requirements for Serving as a PI	5
100.4 Exemption from IRB Approval Criteria	6
100.5 Research Requiring IRB Approval and Oversight	8
100.6 Continuing Review (45 CFR 46.109(e))	11
100.7 Review of Requested Amendments During Approval Period (45 CFR 46.103(B)(4))	12
100.8 Expedited Review	13
100.9 Compliance with Other Applicable Law	15
Special Situations/Exceptions	15
IRB Review required by the Food and Drug Administration	15
Student Projects	15

Scope

This policy describes the types of human subject research, or activities regulated by the Food and Drug Administration (FDA) (e.g., clinical investigation) that must be reviewed by the Institutional Review Board (IRB) prior to initiation. The policy further describes the categories of review exercised by the IRB and the attributes that are required to permit the IRB to carry out each review type.

Policy Statement

The IRB will review human subject research or activities regulated by the FDA to ensure all such research or activities conducted under the auspices of the University meets rigorous ethical standards and all applicable state, federal, and University requirements for the protection of human participants. The IRB will approve human subject research or FDA-regulated activities only if the research or FDA-regulated activity meets the standards defined herein.

Reason for the Policy

University policy 1360 and the following federal regulations require that human subject research, or activities regulated by the Food and Drug Administration (FDA) (e.g., clinical investigations) involving human participants be subject to oversight by an IRB to ensure that the rights and welfare of research participants are protected and that the research, or FDA-regulated activity, meets regulatory and institutional requirements:

1. The Public Health Service Act (PHS) and its amendments compiled in the “Common Rule, 45 CFR 46 subpart A (See related [information](#) on the seventeen federal departments and independent agencies that adopt, codify and expand upon the principles of the Belmont Report)
 - a. 45 CFR 46 subpart B – pregnant women, fetuses, and neonates
 - b. 45 CFR 46 subpart C – prisoners
 - c. 45 CFR 46, subpart D – children
2. The Food & Drug Administration (FDA)
 - a. 21 CFR 50 – human subject protections
 - b. 21 CFR 56 – institutional review boards
 - c. 21 CFR 312 – investigational drugs and biologics
 - d. 21 CFR 812 – investigational devices

3. 28 CFR 512.10 – Department of Justice requirements for research conducted in the Bureau of Prisons.

This policy defines the projects that must be reviewed by and under the oversight of the IRB, the criteria for IRB approval and exemption from the approval requirements of this policy, and identifies when investigators should consult the IRB, or IRB-designated reviewers and/or IRB promulgated guidance in determining when their project requires a formal determination by the IRB that the project does not require IRB approval or oversight.

Definitions

Abstain

Not to vote either for or against a motion before the IRB. An IRB member may abstain from voting for any reason and need not reveal the reason for abstaining.

Clinical Investigation (21 CFR 50.3(a)(25c))

For studies subject to FDA regulations, any experiment that involves a test article and one or more human subjects and that either 1) is subject to requirements for prior submission to the FDA under section 505(i) (Abbreviated New Drug Applications) or 520(g) (device exemptions) of the Food Drug and Cosmetic Act (FDCA) or 2) is not subject to the requirements for prior submission but the results of the experiment are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Demonstration Project

Implementation of a method, technology, policy or idea to assess feasibility prior to full implementation. For example proof of concept studies or the initiation of a benefit or service program or modification of such program for the purpose of assessing its ability to improve the provision of government programs.

Food and Drug Administration (FDA)-Regulated Activities

Activities conducted under the oversight of an IRB that are regulated by the FDA under 21 CFR Part 50, 56, 312, 812 and 814.

Human Subject Research

Projects that meet the definitions of both “research” and “human subject”.

Human Subject or Human Participant

45 CFR 46 (Common Rule definition) –

“A living individual about whom an investigator (whether professional or student) conducting research obtains either (1) Data through intervention or interaction with the individual; or (2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

21 CFR 50.3(g) and 21 CFR 56.102(e) (Food & Drug Administration definition) –An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Human Subject or Human Participant includes individuals who participate as patients in any FDA-Regulated Activities.

Note that both human subject and human participant are used interchangeably in IRB policies and procedures. While the term “participant” conveys the voluntary nature of an individual’s agreement to participate in the research, it also can convey a sense of partnership, which is not reflected in all types of research. In some cases, the research volunteer is in fact more acted upon than truly having any sense of partnership in the research. Hence the term subject is considered more appropriate in such cases.

Individually Identifiable

The identity of the research participant is, or may readily be, ascertained by the investigator or associated with the information.

Institutional Review Board

A University committee established in accordance with 45 CFR 46, 21 CFR 56 and 28 CFR 512.10 which is designated by the University to ensure the ethical and equitable treatment of research volunteers and to protect the rights and welfare of those who participate in research. The IRB has the authority to approve, require modification or disapprove research projects involving human research participants or deem certain projects exempt from, or not requiring, IRB review and oversight.

Minimal Risk (45 CFR 46.102(h)(i))

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.

Minor Change

Changes in the research plan which do not substantively affect risk or benefit of the research. Minor changes may include, for example, changes in research personnel, small changes to wording of questionnaires which do not change the nature of the questions to be asked, insignificant variations to the amount of blood being drawn for a research sample, changes in presentation of materials such as interview to questionnaire format, changes which reduce the number of scans or other procedures that reduce the risks to participants, adding new advertisements, increasing the duration of a study.

National Institutes of Health (NIH) Clinical Trial

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

¹ See Common Rule definition of *research* at 45 CFR 46.102(d).

² See Common Rule definition of *human subject* at 45 CFR 46.102(f).

³ The term “*prospectively assigned*” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

⁴ An *intervention* is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

⁵ *Health-related biomedical or behavioral outcome* is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes;

Private Information

Individually identifiable data 1) about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, or 2) which has been provided for a specific purpose by an individual and which the individual can reasonably expect will not be made public or accessed for research purposes.

Public Benefit or Service Program

A federal, state, or local government initiated or endorsed program to deliver financial or medical benefits such as those provided under the Social Security Act or services to improve public welfare such as social, supportive, or nutrition services.

Recuse

To disqualify oneself from discussion and vote on a protocol by leaving the IRB meeting. Recusals are generally initiated by the IRB member because of a real or perceived conflict of interest in the research under discussion. Recusals remove the member from the total number of members present and thus impact quorum.

Research**45 CFR 46.102(d) (Common Rule – Subpart A) –**

“A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Activities, which meet this definition, constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes.

21 CFR 50.3(g) and 21 CFR 56.102(e) (Food & Drug Administration) –

Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this regulation, regarding nonclinical laboratory studies.

Research subject to regulation (45 CFR 46.102(e))

Research subject to regulation (and similar such terms) is intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

Test Article (21 CFR 50.3(j))

Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Act (PHA) (42 U.S.C. §§ 262 and 263b-263n).

positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

Policy Sections

100.1 Projects Not Meeting the University, Department of Health & Human Services (DHHS) Office of Human Research Protection (OHRP) or Food & Drug Administration (FDA)

Regulatory Definition of Research Involving Human Subjects

Projects which do not qualify as a clinical investigation, “research,” or which do not involve “human subjects” as defined in the federal regulations and University policy are not mandated to be subject to approval and oversight by the IRB. Federal guidance, some federally supported data and tissue repositories and some professional journals, however, require an investigator to demonstrate that an IRB has determined that the activity(ies) was not subject to IRB approval or oversight prior to the project being initiated. The IRB will assist an investigator in making a determination regarding whether or not a project qualifies as a clinical investigation or research involving human participants through consultation and issuance of guidance (see IRB Guidance on QI/QA and IRB Guidance on Humanities Projects and IRB Review). In particular, investigators working with coded data sets derived from humans, or other projects which are not clearly outside the scope of the federal definitions should submit such projects to the IRB for review and determination as to whether or not the project constitutes human subject research requiring IRB oversight. Researchers submitting protocols to the IRB for determination of whether or not the project constitutes a clinical investigation, research or involves human participants will be provided with a written determination from the IRB.

100.2 Research Subject to IRB Review

The IRBs are responsible for ensuring the review of all research or clinical investigations involving human participants, regardless of sponsorship, in which the University is considered to be engaged. The University is engaged in research or clinical investigations and hence the project must be reviewed by an IRB when the project qualifies as human research or a clinical investigation as defined above and when one or more of the following apply:

- the research/clinical investigation is sponsored by the University;
- the research/clinical investigation is conducted, in whole or in part, by members of the University faculty, staff or students acting in their University capacity regardless of the location of the activity, either at Yale or elsewhere in the world;
- the University receives a direct federal award to conduct human subject research/clinical investigation, even where all activities involving human participants are carried out by a subcontractor or collaborator.

Projects that do not involve Yale faculty, staff, and students but involve recruitment targeted at members of the Yale community or use of Yale facilities, and projects conducted by an agent of another institution using any of the University’s property or facilities but not otherwise engaged in human research/clinical investigation at Yale might not be required to obtain approval by the Yale IRB, but must obtain appropriate approvals from those responsible for the relevant subject population or resource. The IRB is available for consultation regarding ethical or regulatory aspects of such projects upon request.

For further information on determining if the University is engaged in research see OHRP guidance on engagement at <http://www.hhs.gov/ohrp/policy/engage08.html>.

The Yale IRBs will ensure review of research for which the University is engaged either through conducting the review or by initiating a formal agreement with another IRB as described in IRB Policy 920 Research Partnerships. Yale IRBs also are responsible for review of research when the research is conducted in accordance with an Assurance approved by the Office of Human Research Protection (OHRP) in which a Yale IRB is designated as the IRB of record through an established IRB Authorization Agreement (“IAA”).

100.3 Requirements for Serving as a PI

The IRBs will accept for review protocols submitted by:

- principal investigators, who are defined by the Yale Faculty Handbook as those employed full-time by the University and hold an appointment as assistant professor, associate professor, professor, research scientist/scholar, or senior research scientist/scholar; and
- students, trainees, and employees conducting research, when they are under the oversight of a faculty advisor who meets the qualifications of a principal investigator as defined above or are otherwise granted an exception to serve as the advisor through the process noted below; and
- graduated Yale students who receive Yale-administered fellowships. This does not include fellowships externally administered (e.g., Fulbright). The recipients of Yale-administered fellowships are not required to have a Yale faculty member provide project oversight.

Exceptions require the approval of the Provost, or where appropriate, the Dean of the relevant professional school (in some cases, the Provost or Dean may delegate the authority to approve exceptions). The request form for School of Medicine and School of Public Health investigators can be found at <http://www.yale.edu/hrpp/forms-templates/biomedical.html>.

In addition, depending on the terms of the IRB Authorization Agreement, the IRBs will accept for review protocols submitted by personnel from non-Yale entities for whom the Yale IRBs serve as IRB of record, in accordance with established investigator vetting and approval procedures conducted by the non-Yale entity (e.g., Yale New-Haven Hospital).

100.4 Exemption from IRB Approval Criteria

Federally funded or regulated human research:

According to regulations at 45 CFR 46 and 21 CFR 56, certain federally-funded or regulated human research activities may be eligible for a determination of exempt status by the IRB or IRB-designated reviewers.

Research of this nature may be considered for exempt status if the only involvement of human participants in the research falls into one of the following categories:

1. Research not regulated by the FDA conducted in established or commonly accepted educational settings, involving normal educational practices such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. 45 C.F.R. § 46.101(b)(1). Such research may not include prisoners as participants under the exemption.
2. Research not regulated by the FDA on adults involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior unless: (i) information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and (ii) any disclosure of the human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation. 45 C.F.R. § 46.101(b)(2). Research involving children may only be considered exempt under this category when the project is limited to education tests or observation of public behavior and the investigator does not participate in the activities being observed. Such research may not include prisoners as participants under the exemption.
3. Research not regulated by the FDA involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not otherwise exempt above if: (i) The human

participants are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. 45 C.F.R. § 46.101(b)(3). Such research may not involve prisoners as participants under the exemption.

4. Research not regulated by the FDA 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 participants cannot be identified, directly or through identifiers linked to the participants. 45 C.F.R. § 46.101(b)(4). Such research may not involve data from persons who are known to be currently imprisoned as participants or have been collected from incarcerated individuals under the exemption.
5. Research and demonstration projects not regulated by the FDA which are conducted by or subject to the approval of a Governmental Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs. 45 C.F.R. § 46.101(b)(5). Such research may not involve prisoners as participants under the exemption.
6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. 45 C.F.R. § 46.101(b)(6), 21 CFR 56.104(d). Such research may not involve prisoners under the exemption.

Unfunded human research:

Yale University Special Exemption Category 7: Research Involving Response to Non-Physically Invasive Stimuli

In addition to the six federal exemption categories above, the IRB or an IRB-designated reviewer grants exemptions under the following seventh category for research that meets the criteria described. This category is an extension of the above category b (2) and **does not exist in the federal regulations under 45 CFR 46.101(b)**:

7. Research involving interviews, surveys, educational test or observation of public behavior in which participant interaction includes providing a response to a non-physically invasive stimulus or behavioral activities commonly performed outside the research context (e.g., reading/writing tasks, minimal risk non-invasive physical activities such as walking, talking and sitting, computer tasks, video games, viewing media, internet searches, holding warm or cold items, etc.) may be determined by the IRB or its designee to be exempt if the following criteria are met:

- The research falls under the purview of the Yale University IRB,
- The research poses no more than minimal risk to participants, and
- The research does not include any of the following:

1. Any funding, including federal funding or federal training grants
2. FDA regulated components
3. procedures that would be considered biomedical based
4. sponsor or other contractual restrictions
5. clinical interventions
6. prisoners as subjects
7. children as subjects
8. receipt of an NIH issued Certificate of Confidentiality to protect identifiable research data.

Researchers submitting projects that they believe qualify for an exempt determination must obtain written notification from the IRB or its designee prior to proceeding with the research. The exempt determination must not be assumed by the investigator without such formal determination from the IRB or qualified IRB-designated reviewer.

A copy of the exemption request and determination will be maintained in the IRB records and members of the relevant IRB will be notified of the study's exempt status.

100.5 Research Requiring IRB Approval and Oversight

A. Requirements for IRB Approval

Human research, which does not qualify for exemption, will be reviewed by the IRB in accordance with Procedures 100 PR1 or 100 PR2. Review will be conducted by individual(s), IRB members and consultants, as needed, who have appropriate scientific or scholarly expertise for adequate review of the proposed research. Research projects will not be approved unless all of the following criteria for approval are satisfied:

- risks to participants are minimized, including physical, psychological, social, legal, or economic;
- risks to participants are reasonable in relation to anticipated benefits;
- selection of participants is equitable and does not inappropriately exclude based on gender, race, age or other criteria;
- informed consent is adequate and appropriately documented; if participants cannot consent for themselves, parental or surrogate consent is obtained in accordance with Policy 310, Participation of Children in Research or Policy 340, Participation of Individuals with Impaired Consent Capacity.
- where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants;
- where appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data;
- appropriate safeguards have been included to protect vulnerable participants;
- where appropriate, payment amounts and methods for study participation are fair and reasonable;
- where appropriate, documented approval has been obtained from cognizant University review committees such as the Pediatric Protocol Review Committee, Cancer Center Protocol Review Committee, and the Yale New Haven Radiation Safety Committee; the IRB will determine whether or not to approve a study pending ancillary committee approval, or withhold consent and other documents until such ancillary committee approval is obtained;

- any additional funding agency requirements for review are met such as confirmation of congruency with funding applications;
- where appropriate, investigator and/or institutional conflicts of interests are appropriately disclosed and considered de minimis, eliminated, or, where found to be a significant financial interest, managed; and
- all persons serving as members of a research team are qualified to perform the research, including having completed training in the ethics of human research and, where applicable, the principal investigator is, or is overseen by, an appropriately licensed professional or by appropriately experienced clinical or research staff. Moreover, an appropriately licensed individual must conduct those interventions for which licensing or certification would normally be required. In addition, if participation in the study includes a reasonable possibility of physical or psychological injury, an appropriately licensed clinician or counselor must be part of the research team or be readily available for referrals.

B. IRB Actions

The IRB may take the following actions with respect to a research protocol submitted for review:

- approval
- specific minor revision required (minor changes or clarifications to the research protocol, the informed consent or other research documents that are identified by the IRB and are required to be addressed by the investigator to secure approval). Note that a protocol, which requires modifications, may not commence until the investigator has been notified in writing by the Committee or single member reviewer that the conditions for approval have been met.
- substantive revision required/deferral of approval (substantive or significant questions and/or concerns that have been identified by the IRB and must be addressed by the applicant investigator and re-reviewed by the fully convened IRB or expedited reviewer, depending on whether or not initial review was conducted by a full board or by expedited review)
- disapproval (proposal does not meet requisite standards)
- suspension of either the research project or discontinuation of the Principal Investigator's permission to conduct the research. Suspension may involve all activities (recruitment, enrollment, treatment, data analysis) or partial (certain activities may continue)
- termination – ending of all activities related to the human subject research project or the permission of a Principal Investigator to conduct the human subject research

In addition, the IRB has the authority to:

- appoint one or more individuals (other than the researcher) to observe the consent process or the research and to report back to the IRB with any findings. The IRB shall appoint such an individual whenever the IRB determines, based on information available such as adverse event reports, potential conflicts of interest, deficiencies noted in the IRB files, or media or scholarly reports of research activity, that monitoring is in the best interests of the human participants; and
- audit protocol activities either at random, when deemed necessary to determine from someone other than the principal investigator that no material changes have occurred since the previous IRB review, or based on available information in accordance with Policy 700: Noncompliance, Suspension and Termination.

C. IRB Notifications

Principal Investigator Notification

Principal investigators and the identified study correspondent, if applicable, are notified in writing of the results of review. When the IRB requests modifications or disapproves, the investigator is informed in writing of the reasons for the IRB's actions. When the research proposal is approved, the investigator is notified of the following:

- requirement to report serious and unexpected adverse events related to the participant's research involvement or unanticipated problems in accordance with Policy 710;
- Requirement to report protocol deviations and noncompliance to the IRB in accordance with Policy 700;
- requirement to obtain approval of any changes to the protocol and/or consent form(s) prior to initiating the proposed changes in the conduct of research;
- the approval period and any constraints on the approval such as a requirement for consent to be monitored or a requirement to provide a progress report to the IRB following enrollment of a limited number of participants; and
- requirement to submit a progress report and request for renewal of approval before the date that the IRB has determined continuing review is required.

Other Notifications

Protocols, which the Investigator informs the IRB are related to a funding proposal or award, will be reviewed by the IRB along with the funding application for congruency. The outcome of this review will be recorded in the IRB protocol database and provided to the Office for Sponsored Projects in accordance with established inter-departmental procedures.

If the protocol involves a research affiliate, the Human Protections Administrator of the affiliated institution will be notified of the approval.

If the protocol involves a Yale research center or other University administrative body which requires notification, such notification will be provided by the IRB when requested by the investigator, research center, or administrative body.

The IRB will also periodically report on review activities to the Institutional Official either by providing copies of or access to the IRB minutes, through activity reports, or verbally in the case of emergent issues.

D. Investigator Response to the IRB following Full IRB Review

Investigators whose studies were not approved by the IRB and who wish to pursue the protocol must respond to IRB actions and stipulations by either modifying the protocol in accordance with the IRB request or justifying why such changes are not warranted. Investigator responses will be reviewed by the IRB as described in IRB Procedure 100PR1, Review by Convened IRB or PR2, Expedited Review, as appropriate. Failure to respond to the IRB request(s) in a timely manner will lead to the protocol being withdrawn (if never initially opened) or administratively closed by the IRB. Investigators will be contacted by the IRB prior to withdrawal or administrative closure, reminding them of the outstanding request by the IRB.

E. IRB Records

The IRB will maintain a copy of the protocol and related documents (applications, scientific review documents, DHHS-approved sample consent forms if applicable, reports of injuries, continuing review documents, and statements of any significant new findings provided to subjects) and all correspondence between the IRB and the investigators for a period of at least three years

following completion or closure of the study whether or not any subjects have actually been enrolled.

Deliberations and findings by the convened IRB will be recorded in meeting minutes and retained in accordance with Guidance 100 GD.12, IRB Minutes. Minutes and protocol correspondence will be made available to the Institutional Official and representatives of funding or oversight agencies as appropriate.

100.6 Continuing Review (45 CFR 46.109(e))

Federal regulations require that the IRB conduct continuing review of each approved protocol at intervals appropriate to the degree of risk and not less than annually (i.e., on or before the anniversary of the previous IRB approval). In general, the approval period begins on the date the submission is approved by the IRB and expires 364 days later, which is the last date of the approved period. For example, a proposal approved on 1/15/2012 will expire on 1/14/2013. The IRB may, in its discretion, require more frequent reviews (e.g., where warranted by the magnitude of risk presented to persons participating in the protocol; the population involved; uncertainties about the expected risks such as pilot studies or administration of novel drugs; or for other reasons deemed necessary by the IRB) and will document its determination in the minutes of the meeting. The letter of approval will specify the expiration date of IRB approval. The IRB may determine that a renewal period shorter than one year is appropriate given the nature of the study, IRB requirements, or specific milestones that must be met and evaluated by the IRB before extending the study's duration. The IRB may also determine that a renewal period longer than one year is appropriate if the protocol qualifies for an extended (two-year) renewal period (see Guidance on Approval and Expiration Dates, 100 GD2). The Principal Investigator is required to submit an annual renewal request unless the research is to be closed prior to expiration. The PI who elects to close his/her study should notify the IRB via 100 FR 5C Request to Close.

Study Closure

A local study or multi-center study where Yale University is the lead or coordinating site is eligible for closure if it meets all of the following criteria:

1. The PI has completed enrollment and data collection;
2. The PI and his or her research personnel no longer have any contacts or interactions with the subjects, including long-term follow up; and
3. Analysis of identifiable data is complete and, if a manuscript or presentation is planned, there is no possibility of further data analysis requests (i.e., acceptance of publication or presentation).
4. The investigator submits the completed YALE UNIVERSITY (HIC/HSC) Request to Close form.

The Yale University Request to Close form may be reviewed via expedited review procedures. (Refer to Yale University HRPP policy and procedure, 100 PR 2 [Expedited Review](#))

IRB Chair (or designee) reviews the Yale University (HIC/HSC) Request to Close form using the Request by Investigator to Close a Study Review Worksheet. A communication documenting the IRB's determination is generated and sent to the investigator, and filed in the Yale University (HIC/HSC) protocol file.

If continuing review information is not provided to the IRB or the IRB has not approved the protocol by the expiration date, the protocol is administratively closed by the IRB within a set time-frame established by the HRPP. The IRB may evaluate on a case-by-case basis the ability to re-open a closed study. All activities must stop, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, collection of private identifiable

information, and data analysis of identified data. (See **Procedure 700 PR5: [Expiring or Expired Yale Institutional Review Board \(IRB\) Approval](#)**). Interventions and/or interactions with current subjects may only continue upon appeal by the principal investigator to the IRB, and only if the IRB finds an overriding safety concern or ethical issue which makes continuation of the subject in the research to be in the best interest of the currently enrolled subject. (See 100 FR 22: Protocol Exception Form.) In no case may new subjects be enrolled prior to re-approval of the project by the IRB.

To ensure that continuing review is substantive and meaningful, requests to continue or reapprove a research project will be reviewed at a meeting of the fully convened IRB or by a duly qualified single member reviewer if the research qualifies for expedited review (see Procedure 100 PR1: [Review by a Full Convened IRB](#) and Procedure 100 PR2: Expedited Review).

Requests for renewal of approval will be reviewed by an individual with appropriate expertise to determine the level of IRB review that is required.

The IRB applies the same criteria for review and approval in continuing review as it does in the initial review (i.e., acceptable risks, potential benefits, appropriate consent process and safeguards for human participants). The IRB will assess the current risk level of the project and, if necessary, revise the risk level (decrease or increase) commensurate with the activity being conducted and require any other changes warranted in light of the changes in risk level.

The same actions taken by the IRB that require major substantive revisions or stipulate minor revisions apply to continuing review as described above for initial review.

As part of continuing review, the IRB has the authority to appoint one or more individuals (other than the researcher) to observe the consent process or the research activity and to report back to the IRB with any findings. The IRB shall appoint such an individual whenever the IRB determines, based on information available such as adverse event reports, potential conflicts of interest, deficiencies noted in the IRB files, or media or scholarly reports of research activity, that monitoring is in the best interests of the human participants. The IRB may also audit protocol activities either at random, when deemed necessary to determine from someone other than the principal investigator that no material changes have occurred since the previous IRB review, or based on available information in accordance with Policy 700 Protocol Deviations and Noncompliance.

100.7 Review of Requested Amendments During Approval Period (45 CFR 46.103(B)(4))

University policy, as well as federal regulations, requires prompt reporting to the IRB of proposed changes (amendments) to the research project. Approval by the IRB must be obtained before the change is implemented in the conduct of research. Examples include changes in participant population, dosing, recruitment plans, advertising materials, consent requirements, research procedures or their frequency, study instruments, study sites, or investigators and study personnel.

New information that may affect the risk/benefit assessment must be promptly reported to, and reviewed by, the IRB to ensure adequate and continued protection of human participants.

Minor changes proposed to be implemented during the current IRB approval period may be approved by the IRB via expedited review. Other changes must be reviewed and approved at a meeting of the convened IRB before the changes can be implemented. An exception is made in the rare circumstance in which a change without approval is necessary to eliminate apparent immediate hazards to the research participants. In such case, the principal investigator should alert the IRB chair as soon as the immediate and necessary change is to be made, and follow through promptly with a written amendment for the IRB to review and approve post-facto.

Single Subject Protocol Modification (Prospective Protocol Deviation)

Federal Food and Drug Administration (FDA) IND regulations at 21 CFR 312.66 require that the investigator not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. The FDA IDE regulations at 21 CFR 812.150(a)(4) require that the investigator notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan. If these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval of FDA and the IRB, in accordance with 812.35(a), also is required. The IRB regulations at 45 CFR 46.103(4), 21 CFR 56.108(a)(3) and (4) require the IRB to follow written procedures for ensuring prompt reporting to the IRB of changes in research activity, and for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

In a non-emergent situation in which the investigator intends to deviate from the approved protocol to accommodate current or potential subjects, investigators must submit a Single Subject Protocol Modification form (100 FR29) for any such planned deviation to the protocol. This form, accompanied by a letter of concurrence from the sponsor, must be submitted to the IRB prior to implementation of the planned excursion from the protocol.

[NOTE: If the investigator is also the sponsor, Form 100 FR29 may not be used. An amendment must be submitted.]

Upon receipt of the request for a single subject modification, an IRB Chair will review the request and respond to the investigator in writing. Every effort will be made to respond to each request within 24-48 hours unless full board review is necessary. *Except in instances where action is necessary to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), this procedure may not be used more than once per study (protocol) for each deviation.* If the investigator finds that the single subject modification is necessary to the further safe conduct of the study, the sponsor should be contacted to formally amend the study.

100.8 Expedited Review

Under federal regulations (45 CFR 46.110, 21 CFR 56.110), certain research proposals may not require review by a fully convened IRB, and may be reviewed by the Chair or one or more experienced reviewers designated by the IRB Chair from among members of the IRB through an expedited review process. Investigators submitting research proposals that they believe may qualify for expedited review are to complete the same application and information submitted to the IRB for full Committee consideration. Review of a research project through expedited review must meet all the requirements described in Policy Section 100.5 above with the exception that a study cannot be disapproved through the expedited review process.

Research projects that meet all applicable criteria and represent one or more of the categories below may be reviewed through an expedited review process. In some cases, however, the expedited reviewer may submit the project to the full board if in his/her opinion, the expertise of the full board would be useful to the comprehensive review. IRB records will include documentation regarding the determination of permissible category as described below:

A) Minor changes proposed for previously approved research during the period (one year or less) for which approval is authorized. Changes significantly increasing risk or decreasing benefit are not "minor" changes. For example, minor changes include changes in research personnel, small changes to wording of questionnaires which do not change the nature of the questions to

be asked, minor variations to the amount of blood being drawn for a research sample, changes in presentation of materials such as interview to questionnaire format, changes which reduce the number of scans or other procedures that reduce the risks to participants, adding new advertisements, increasing the duration of a study; or

B) Research reviewed by a fully convened IRB which has determined that approval may be granted if one or more specific minor revisions is made and the review is to confirm that the requested changes were implemented or an IRB-determined acceptable justification for not implementing the change(s) has been provided by the PI; or

C) Research which appears on the list below and which is found by the reviewer to involve no more than minimal risk:

1. Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (i) from healthy, nonpregnant adults who weigh at least 110 pounds. For these participants, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or (ii) from other adults and children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.
3. Prospective collection of biological specimens for research purposes by noninvasive means such as: (i) Hair and nail clippings in a nondisfiguring manner; (ii) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (iii) permanent teeth if routine patient care indicates a need for extraction; (iv) excreta and external secretions (including sweat); (v) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (vi) placenta removed at delivery; (vii) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (viii) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (ix) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (x) sputum collected after saline mist nebulization.
4. Collection of data using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve the input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, electroretinography, MRIs at 7T or less and ultrasound. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves). Studies intended to evaluate the safety and effectiveness of a medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.
5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. 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.
8. Continuing review of research previously approved by the convened IRB that is limited to one or more of the following:
 - a. Research where (i) the research is permanently closed to the enrollment of new participants; (ii) all participants have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of participants.
 - b. Research where no participants have been enrolled and no additional risks have been identified.
 - c. Research where the remaining research activities are limited to data analysis.
9. Continuing review of research not conducted under an investigational new drug application or investigational device exemption where the research does not otherwise qualify for expedited review but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The IRB members will be notified of all studies approved under the expedited review procedure.

100.9 Compliance with Other Applicable Law

In addition to the requirements described herein, specific research projects may invoke additional state and/or federal laws or regulation as well as additional University policies. Research projects are required to comply with any additional requirements described in such applicable laws, regulations or policies. A description of potentially applicable laws and regulations is provided in IRB Guidance 100 GD7.

Special Situations/Exceptions

IRB Review required by the Food and Drug Administration

The IRB is also involved in the oversight of Investigational New Drug (IND) and Investigational Device Exemption (IDE) clinical trials, Humanitarian Use Device (HUD) studies, Emergency Use or Expanded Access Use research and Exception From Informed Consent (EFIC) research. IRB review requirements related to these activities are described in IRB Policy 600.

Student Projects

Student projects including projects conducted as a course requirement such as methods courses may not meet the definition of research in that the projects are unlikely to produce generalizable knowledge. The Human Research Protection Program may nonetheless choose to have the IRB review these projects for the purpose of 1) educating students on the ethical and regulatory requirements for the conduct of research and 2) ensuring that these educational activities do not inappropriately expose individuals to risk of harm.

Related Information

HRPP Policy 700: Noncompliance, Suspension and Termination

100 PR.1: Review by Convened IRB

100 PR.2: Expedited Review

100 PR.3: Exemption Determinations

700 PR5: [Expiring or Expired Yale Institutional Review Board \(IRB\) Approval](#)

100 GD.1: Humanities Research and IRB Review

100 GD.2: Approval and Expiration Dates

100. GD.7: State and Federal Laws or Regulations Related to Human Research

Contacts

Subject	Contact	Phone e-mail
IRB Review of Biomedical Research	Human Investigation Committees	203-785-4688 HRPP@yale.edu
IRB Review of Social Science, Behavioral, Education and Humanities Research	Human Subjects Committee	203-785-4688 Human.subjects@yale.edu

Roles and Responsibilities

Human Investigation Committee

The HIC I, HIC II, HIC III and HIC IV serve as the four Institutional Review Boards or IRBs for biomedical human research conducted at Yale University.

Human Subjects Committee

The HSC serves as the Institutional Review Board or IRB for social, behavioral and educational research conducted at Yale University.

Revision History

Modified 05/05/2010, 05/04/2010, 05/11/2009,
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