

Oversight of Yale Sponsor-Investigator held Investigational New Drug (IND) Applications, Investigational Device Exemptions (IDE) or Emergency Use Authorizations (EUA)

Responsible Officials

Dean, Yale School of Medicine and Deputy Dean for Clinical and Translational Sciences, Yale School of Medicine, including Public Health

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Responsible Offices

Yale Center for Clinical Investigation

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Scope

This policy applies to Yale School of Medicine investigators who hold, or are considering holding with the Food and Drug Administration (FDA):

- Investigational New Drug Applications (INDs) including Compassionate use/Expanded access
 - Investigational Device Exemptions (IDEs) including Compassionate use/Expanded access
 - Emergency Use Authorizations (EUA)
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Purpose of the Policy

The purpose of this policy is to establish oversight and reporting requirements for Yale Sponsors and Sponsor-Investigators of INDs, IDEs or EUAs.

Policy Statement

Yale is committed to ensuring compliance with all applicable laws, regulations, guidelines, and university requirements regarding the conduct of human research including adherence to FDA regulations.

The Yale Center for Clinical Investigation (YCCI) IND/IDE Management Office is established to review and approve all Yale proposals to be performed under a Yale-held IND, IDE, or EUA. The YCCI Oversight Committee was established to provide broad oversight of clinical research management practices, including

of Yale Sponsor and Sponsor-Investigator held INDs and IDEs.

The Sponsor-investigator of an IND or IDE application is an Investigator who is responsible for the design of a clinical investigation and is qualified by training and experience to oversee the conduct of the clinical investigation. A Sponsor-Investigator who holds an IND/IDE must comply with investigator responsibilities as well as additional sponsor responsibilities such as project coordination, data management, and study monitoring.

In certain situations, the Sponsor of the IND or IDE application and the study site Investigator may be different individuals (e.g., the faculty member responsible for the design of the clinical investigation has a financial conflict-of-interest related to the test article being evaluated in the clinical investigation). Under this scenario, the designated Sponsor of the IND or IDE application is subject to compliance with the FDA regulations governing the responsibilities of the Sponsor of an IND or IDE application and the Investigator is subject to compliance with the FDA regulations governing the responsibilities of a study site Investigator. Note that this latter scenario creates certain documented reporting requirements between the Sponsor and the Investigator, even though these two individuals may be located within the same academic unit.

Emergency Use Authorizations are an FDA authorization to distribute a product pursuant to a declared public health emergency. The sponsor of the EUA must comply with the terms of authorization, including labeling and distribution, reporting and record keeping, compliance with advertising and promotion, and requirements around requesting changes to the EUA. Although emergency use authorized products are not considered to be “approved” or “cleared” drugs, biologics, or devices, they can be made available and/or commercialized like an approved product, within the terms of authorization. As such, there is a significant responsibility in sponsoring an EUA.

Definitions

YCCI Oversight Committee (the “Committee”)

Yale School of Medicine (YSM) Dean’s Office appointed committee comprised of the YCCI Co-Directors and Deputy Directors charged with the development of clinical research policy; broad oversight of clinical research management practices; approval of YCCI Quality Assurance Review plans and activities; and the monitoring of broad acceptance and compliance of the YSM faculty with new research guidance/policy.

Emergency Use Authorization (herein referred to as “EUA”)

Application submitted to the FDA to facilitate the availability of medical products including drugs, biologics, or devices as medical countermeasures for the treatment, prevention, or diagnosis of chemical, biological, radiological, and nuclear agents, including emerging infectious disease threats. An authorization allows the distribution of such products for specified authorized uses during the period of the declaration of a public health emergency. An EUA application requires the submission of data to support the safety and effectiveness of the use of the product, and quality of manufacturing, which meet any requirements FDA may set for such an application.

Expanded Access/Compassionate Use

A potential pathway for patients with a serious or life-threatening disease or condition to access an investigational drug or device to treat, prevent, mitigate, cure, or diagnose the condition, outside of clinical trials and when no comparable or satisfactory alternative therapy options are available. The different types are:

- **Emergency single-patient:** use of the product when an individual patient is in a life-threatening situation, needs immediate treatment, and FDA approval must be obtained by informal rapid communication (e.g., acute mushroom poisoning)
- **Single-patient:** Use of the product in an individual patient, when a clinical trial is not available or the patient does not qualify for available trials. This pathway is also sometimes also used to continue subjects on treatment after a clinical trial ends.
- **Intermediate-size or Treatment/Widespread Use:** Provides access to an investigational product for use by more than one patient. These programs may not substitute for clinical trials to collect data to determine the safety or efficacy of the unapproved product.

Food and Drug Administration (herein referred to as “FDA”)

The United States regulatory authority which oversees the pharmaceutical and medical device industries and is

responsible for ensuring that the drugs and medical devices marketed in the U.S. have a greater benefit than risk when used according to manufacturer's directions.

Investigational Device Exemption (herein referred to as "IDE")

Prescribed documents/application submitted to the FDA to allow for the conduct of a clinical study using a significant risk device that is new or not approved for that use. Non-significant risk IDEs are not submitted to FDA but do have other IDE responsibilities. For purposes of this policy, IDEs include Compassionate Use/Expanded Access IDEs.

Investigational New Drug Application (herein referred to as "IND")

Prescribed documents/application submitted to the FDA to allow for the conduct of a clinical study using a drug that is new or not approved for that dosage, form, or indication. For purposes of this policy, INDs include Compassionate Use/Expanded Access INDs.

Investigator

An individual who conducts a clinical investigation (i.e., under whose immediate direction the drug or device is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. (ICH GCP E6 (R2)).

Quality Management

Quality management is the act of overseeing all activities and tasks that must be accomplished to maintain a desired level of excellence. This includes the determination of a quality policy, creating and implementing quality planning and assurance, and quality control and quality improvement. Yale Human Research Protection Program (HRPP) and the Yale Center for Clinical Investigation QA and Monitoring units are components of the quality management processes for YSM.

Sponsor

A person or an organization who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator

An individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug or device is administered or dispensed. A Sponsor-Investigator must comply with all the obligations of both a Sponsor and an Investigator.

Yale School of Medicine (herein referred to as "YSM")

Yale School of Medicine includes Yale School of Medicine, Yale School of Public Health and Yale Medicine.

Policy

A Yale Investigator who intends to conduct an investigation/project that requires an IND, IDE or EUA must submit for review to the YCCI IND/IDE Management Office. The Office must receive IND/IDE/EUA applications either before or contemporaneously with their submission to the FDA and the Yale HRPP for IRB review, as applicable. Submissions of proposals to the HRPP requiring an IND/IDE that have not been previously reviewed or approved by the Office will be routed to the Office by the HRPP prior to IRB review and approval. Emergency INDs/IDEs will be reviewed by the Office within 48 hours of completion of all necessary documentation. Approved projects may be referred to YCCI clinical study operational teams for assistance with development, upfront submission and ongoing maintenance of the IND/IDE/EUA.

Requirements pertaining to all types of applications include:

- Inclusion of the YCCI IND/IDE Management Office in all contacts with the FDA, including preliminary discussions.
- YCCI IND/IDE Management Office must review and maintain a copy of all IND/IDE and EUA submissions to FDA.
 - The Office will maintain documents, including copies of the application, communications, safety reports, amendments, and annual reports; remind sponsor-investigators of their reporting obligations to the FDA; and track reports and communications with the FDA.
 - Sponsor must ensure the YCCI IND/IDE Management Office is named as an Authorized Point of Contact and ensure the YCCI IND/IDE Management Office is provided copies of all communications from the FDA.
- Assurance of ethical, scientific, and data integrity through the lifecycle of the proposed research. This includes the requirement to provide a recruitment strategy such as a method for meeting study objectives in an appropriate timeframe and consideration of diversity including inclusion of underrepresented groups in the research.
- Documentation of sufficient funding and resources to support Sponsor-Investigator responsibilities and clinical protocols incorporated into the IND or IDE
- Disclosure of all Conflicts of Interest per University policy and Federal regulations.
- Completion of required initial Yale training program for faculty and staff engaged in IND, IDE or EUA projects, and at least yearly recertification by IND/IDE Management Office.
- Manufacturing practices per University policy and Federal regulations as applicable.

Requirements pertaining only to applications under which clinical research is conducted include:

- Development of an operations plan including:
 - Project management and monitoring to meet regulatory requirements; and
 - Use of HIPAA and 21 CFR Part 11 compliant systems and other mandated research systems.
(Note: Inability to provide and execute a compliant plan will trigger necessary use of YCCI services at sponsor expense or otherwise result in project termination.)
- New protocols added to an existing IND or IDE application are required to follow the submission process per this policy including receipt of YCCI IND/IDE Management Office approval before proceeding.
- In cases where the IND/IDE Sponsor is different from the Investigator, the Sponsor must ensure the designated study site Investigator for the conduct of the clinical protocol is incorporated into the IND or IDE application and is aware of and possesses the appropriate qualifications and experience to be able to comply with the regulatory responsibilities of an IND or IDE Investigator.
- An IND/IDE Sponsor planning the conduct of a multi-center clinical investigation under a University-based IND/IDE application must include sufficient funding to address all regulatory responsibilities associated with being an IND/IDE Sponsor and must establish appropriate processes and corresponding written procedures directed at addressing these responsibilities. The existence of these processes and procedures and the adequacy of available funding to support these processes will be major considerations in the decision to permit the involvement of external study sites under a Yale Investigator-based IND or IDE application.

The YCCI IND/IDE Management Office may refer proposals to the YCCI Oversight Committee for further adjudication or action. This group has been charged to provide general oversight of all proposed projects to be completed under an IND/IDE/EUA for feasibility, resources, budget, project management, monitoring and data management prior to full development of the IND or IDE application and protocol. The YCCI Oversight Committee may gather input from Clinical Investigators, Department Chairs, Center Directors, Section

Heads, General Counsel's Office, Provost's office, Dean's Office, Yale Center for Analytical Sciences (YCAS), Investigational Drug Service (IDS), Yale New Haven Health System (YNHHS), in establishing guidance on any referred proposals.

Active research under Yale INDs/IDEs will be reviewed by the YCCI Oversight Committee on an ongoing basis allowing for overall oversight, including but not limited to accrual monitoring, safety monitoring, and evaluation of Corrective and Preventative Actions (CAPAs) where applicable. If protocols are conducted under Yale Sponsor or Sponsor-Investigator INDs or IDEs and have been identified as not meeting applicable FDA and other regulatory requirements, guidelines, and/or University requirements by internal quality management processes, the Committee has the authority to mandate remedial training, require the implementation of a CAPA, temporarily pause enrollment, or if deemed necessary, to permanently close any studies conducted under an IND or IDE. The Committee functions in close collaboration with the YCCI IND/IDE Management Office, the Yale HRPP, and IRB-of-record, in an effort to ensure the efforts augment and compliment, not duplicate, the work of the HRPP/IRB.

The policy and any updates will be maintained via the YCCI and HRPP websites (YCCI@yale.edu; HRPP@yale.edu). Additionally, the policy will be provided administratively to Chairs, Chiefs and Lead Administrators for faculty and research staff distribution. Lastly, the HRPP will share the policy with all current principal investigators of HRPP-approved protocols.

Roles and Responsibilities

Yale Center for Clinical Investigation Oversight Committee

- Authority to oversee the conduct of clinical/translational studies to ensure the safety of participants and to maintain the highest quality of clinical research.

Sponsor-Investigator

- Ensures the research study is conducted according to the IRB-approved protocol and in accordance with University policies; federal, state, and local regulations; terms of the sponsored award/investigator statement; and other applicable regulations.

Yale Center for Clinical Investigation IND/IDE Management Office

- Provides guidance and support to investigators regarding the development and maintenance of IND and IDE submissions and conduct of research under them.
- Serves as liaison for communication between the FDA and investigators who hold INDs, IDEs, or EUAs.

Related Information

- HRPP Policy 1000 Clinical Trial Registration and Reporting Requirements

Contact Information

- Human Research Protection Program: 203.785.4688. Email: HRPP@yale.edu
- Yale Center for Clinical Investigation: 203.785.3482. Email: YCCI@yale.edu
- Clinical and Translational Research Oversight Committee: Email: ctroc.ycci.committees@yale.edu

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