Yale *Human Research Protection Program*

IRB Submission Form

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Training Goals:

Empower participants to think critically about how to successfully complete the form by:

- Identifying why we need the information and what it is used for.
- Providing rationale for certain complicated sections.
- Pointing out where we don't always ask for (or get) the information we need.
- Providing tips based upon experience with common errors, etc.

Learning Objectives

We hope that you will leave our presentation understanding:

- Why the information is needed.
- What to know that's not apparent from the form.
- How you can help us, help you gain faster approval.

Training Agenda

Agenda Item	Slide #
Why is the IRB Submission Form Needed?	5-9
IRB Submission Form Sections 1-6	10-20
Special Populations & FDA Sections	21-33
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Why is the IRB Submission Form needed?

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Purpose of the IRB Submission Form

- A submission form must be completed and submitted for review to the Yale IRB along with a research protocol for most non-exempt research.
- Note: the submission form does not need to be completed for research utilizing Request for Medical Record Review form, Request for Secondary Data Analysis, Humanitarian Use of Device submissions, Expanded Access protocols, exempt research, or request that the study does not meet criteria for human subjects research.
- This document DOES NOT replace a study protocol.

Purpose of the IRB Submission Form

- Describes how the research will be conducted at Yale e.g., differences between the protocol and what will happen at Yale, specifies recruitment at Yale, includes requests for waivers of consent and HIPAA Authorization.
- While the protocol should include a general information about the study, the IRB Submission Form details how the study is conducted at Yale and spells out the regulatory requirements for specific issues.
- HOT TIP: If the IRB Submission Form asks for information that is already contained in the protocol, simply refer to the section of the protocol. It is not necessary to copy information from the protocol.

Where to upload

- The completed form must be uploaded under the Local Site Documents: Other Attachments as the 'IRB Submission Form'.
- Select IRB Submission Form as the Category.

- Note that documents uploaded as Other Attachments (e.g., IRB Submission Form, Unaffiliated Investigator Agreements, Special Permission to Serve as the PI, etc.) do not receive any watermarks upon approval.

Helpful Hints

- Review submission form for sections that are required and supplemental sections that are applicable to certain types of research only.
- Don't delete sections, even if they do not apply to the current study.
- If the protocol addresses the questions with sufficient detail, reference the section of the protocol. Do not copy and paste the responses from the protocol.
- Read instructions and the information in the blue text boxes.
- Be consistent. What's written in this form should match the protocol and consent.
- Provide additional detail where indicated.

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IRB Submission Form Sections 1-6

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Table of Contents:

- Read through the table of contents. This will direct you to the required and supplemental sections of the form.
  - Helpful hint: Read through the "When to Complete" column, as this contains information about what is in each section and when it applies.
- Complete the checklists column. Don't leave boxes unchecked.

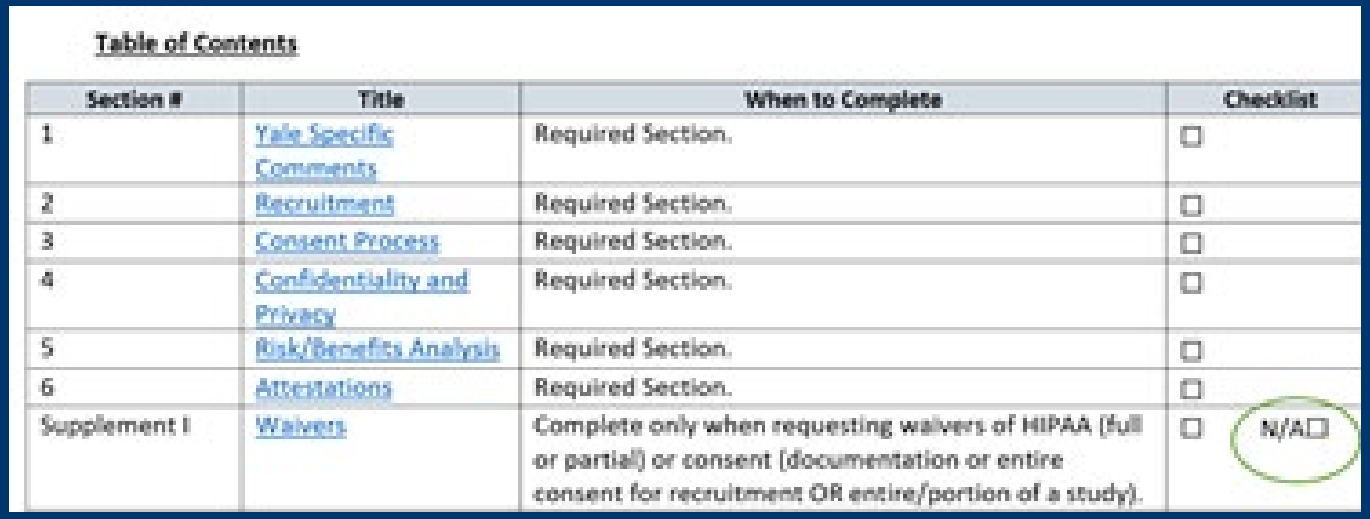


Table of Contents

Section #	Title	When to Complete	Checklist
1	Yale Specific Comments	Required Section.	☐
2	Recruitment	Required Section.	☐
3	Consent Process	Required Section.	☐
4	Confidentiality and Privacy	Required Section.	☐
5	Risk/Benefits Analysis	Required Section.	☐
6	Attestations	Required Section.	☐
Supplement I	Waivers	Complete only when requesting waivers of HIPAA (full or partial) or consent (documentation or entire consent for recruitment OR entire/portion of a study).	☐ N/A☐

Section 1:

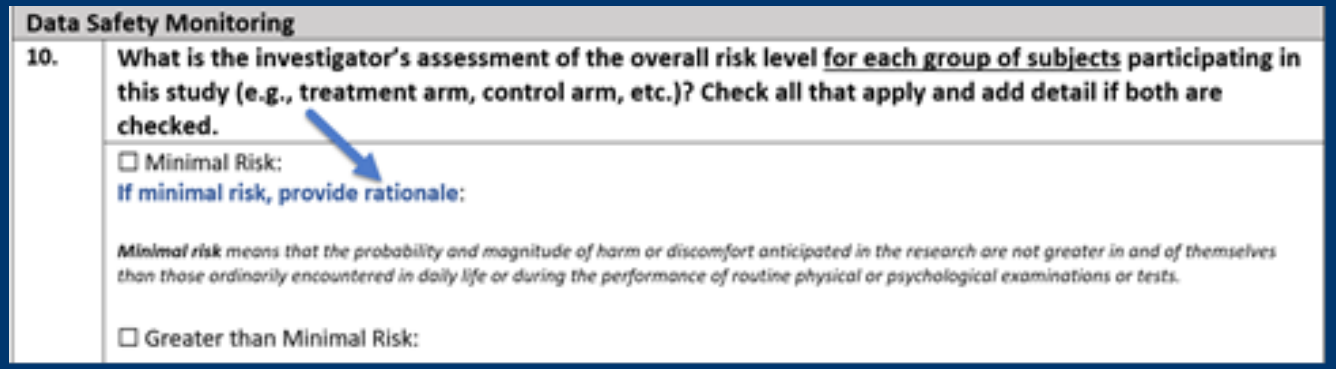
- This section asks about how the protocol will be implemented at Yale/Yale New Haven Health System.
- Any differences between the research protocol and its implementation at Yale/YNHHS must be noted here, if not mentioned in the protocol.
  - For example, if the Yale site will not be enrolling minors, but other sites are, it should be noted in question 2 of this section.
- Again, if this information is already written into the protocol, it is best to provide the page number where the question is addressed.
  - Do not provide different information- requiring us to review both document sections. This leads to confusion.

Section 1 Continued:

- Standard of Care vs. Research (questions 5-9):
  - This section is very helpful to the IRB to determine what procedures are included in the research.
  - By identifying which procedures are conducted for research purposes only, rather than included in clinical care, a determination of the risk level and study benefits can be made more efficiently.
  - Include any risks added by altering or withholding the standard of care.

Section 1 Continued:

- Data Safety Monitoring:
  - Question 10 asks the investigator to assess the overall risk level of the protocol for each group of subjects.
  - If the study is minimal risk, provide the rationale for this assessment here.
  - Question 11 asks about the data and safety monitoring plan (DSMP). It is broken down by risk level (minimal and greater than minimal).
  - The HRPP has template language for the DSMPs linked within the Submission Form.



Data Safety Monitoring	
10.	**What is the investigator's assessment of the overall risk level <u>for each group of subjects</u> participating in this study (e.g., treatment arm, control arm, etc.)? Check all that apply and add detail if both are checked.**
	☐ Minimal Risk: **If minimal risk, provide rationale:** ***Minimal risk*** *means that 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.* ☐ Greater than Minimal Risk:

Section 2: Recruitment:

- In this section, you should provide information about the identification and recruitment of subjects.
- You should describe the process for identifying, contacting subjects, and retaining research participants and indicate if there is an existing clinician relationship with potential subjects.
  - As with other sections, citing the protocol page is acceptable.
- HIPAA waivers are necessary if you are accessing or using protected health information without authorization from the individual. Refer to HIPAA Waivers section.

The use of JDAT services is generally required for the review of medical records at YNHHS and Yale Medical Group.

Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx.

Section 3: Consent Process

- This section contains questions about the consent process used to enroll participants into the study.
- If the study has multiple aims, some obtaining consent, some requesting a waiver, be sure to indicate that in question 1 of this section.
- If eConsent is utilized, note this in question 2 and provide the platform to be used.
- Question 4 asks who will provide consent. It is important to note that if you will be enrolling vulnerable populations who cannot consent for themselves, Supplement VIII must be completed to include the process of obtaining consent/assent/permission for these subjects.

Section 4: Confidentiality and Privacy

- Questions 1-3 in this section describe how the data will be collected and recorded, as well as how identifiers are protected.
- Questions 4-8 describe data storage and access.
  - Helpful hint: Question 5 asks how long both identifiable (coded) and deidentified (anonymized) data will be kept at Yale.
- Question 10 refers to the privacy of the research participants, asking for details regarding the setting of the research intervention or observation.
  - If not described in the protocol, indicate here any provisions taken to protect subject privacy.

Section 5: Risk/Benefit Analysis

- Benefits:
  - List any direct benefits to subjects here.
  - If there are no direct benefits, there must be a benefit to society.
- Risks:
  - Describe the anticipated risks of the research study.
  - The risks of clinical care do not need to be listed here, unless the study randomizes participants to the standard of care versus experimental procedures or to more than one standard of care.

- As previously mentioned, you can cite the protocol page that describes the risks and benefits here to avoid inconsistencies across documents.

Section 6: Attestations

- Be sure to read through these statements, as these are your attestations that you conduct the research study in a way that meets regulatory criteria and institutional policies.
- These attestations should be answered with reference to the protocol at Yale and the responsibilities of the Yale investigators.

Section 6. Attestations	
By submitting this form to the IRB, the Principal Investigator attests to the following. Please, check off the attestations to document your agreement.	
☐	The information provided in this application is complete and accurate.
☐	I assume full responsibility for the protection of human subjects and the proper conduct of the research.
☐	Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
☐	The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.

Supplement 1: Waivers

- Think critically about these sections and answer the questions for the waiver requested and not necessarily for the entire study.
  - For example, a waiver of HIPPA for recruitment only
- Consider for example-

Impracticable to conduct the research means is not feasible or possible to conduct the research with the requirement of obtaining or documenting informed consent/HIPAA authorization given the available resources and circumstances. It's not about absolute impossibility, but rather about the significant challenges and burdens that obtaining consent would place on the research process.

➢ Tell us why, so we can 'determine' it to be the case.

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Special Populations & FDA sections

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The Supplements

- Provide the IRB with information needed that is not always found in the other documents.
- Some supplements are clearer than others
- I won't cover all fully and will go out order

Special Populations	Complete only if the proposed research involves vulnerable populations: minors, prisoners, pregnant women, or decisionally impaired individuals.
Drugs	Complete only when the proposed research includes drugs.
Devices	Complete only when the proposed research includes devices. **This includes assays (saliva and blood) and sequencing platforms.**
Research with Tobacco Products	Complete only when the proposed research includes the use of tobacco products.
Research with Radiation	Complete only when the proposed research includes ionizing radiation.
Research with Cold Isotopes	Complete only when the proposed research includes use of unapproved cold isotopes.
Research Under an IND or IDE Held by a Yale Investigator	Complete only if the proposed research involves use of a drug conducted by an IND held by Yale investigator or it is a device study conducted under an IDE held by the Yale/Yale New Haven Health System (YNHHS) investigator.

Vulnerable and other special populations

minors, prisoners, pregnant women, decisionally impaired individuals, Students, employees, non-English speaking

Why is this section important?

- Enrollment of these participants requires additional protections and often specific, additional determinations.
- Designed to provide the IRB with the information needed to determine whether criteria for inclusion of these populations is met.
- Information not likely to be provided naturally in a sponsored protocol or the NIH style protocol templates in use at Yale.

Supplement VIII	Special Populations	Complete only if the proposed research involves vulnerable populations: minors, prisoners, pregnant women, or decisionally impaired individuals.	☐ N/A☐

Vulnerable and other special populations

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Why is this section important?

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Examples in those 'cognitively impaired' (including subjects with temporary impairment)

- Do they have a disease or condition for which the procedures involved in the research hold out a prospect of direct benefit to the individual subject that is unavailable outside the research context.
- The objectives of the trial cannot be met by means of studying subjects who can give consent personally.
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

The Colon Mystery…..

What is your assessment of risk for each group of subjects participating in this study (treatment arm, control arm, etc.)? Check all that apply.

☐Not greater than minimal:
☐Greater than minimal:
☐Minor increase over minimal risk:

Is there a prospect of direct benefit to minor participants? Check all that apply and specify per group if applicable.

☐YES:
☐NO:

Minors Supplement

From Vulnerable populations / Cognitively impaired criteria

Assent will be obtained from:

☐ All subjects, describe:
☐ Some subjects, specify:
☐ None of the subjects, justify:

- What are they asking?!
- Why leave them empty?

➢Completion tip: They *generally* mean something is required.

Drugs Supplement

SUPPLEMENT III
Drugs
This section is required if the research involves administering a drug for research purposes.

In simple terms…

- The regulation around use of drugs in research requires the vast majority to be **included as part of the research** even if they aren't being studied. [this is different than devices]
- Drugs are either exempt from IND requirements, *or they require an IND.* The supplement provides the IRB with the information to determine what **regulatory criteria** are met or need to be met.
  - *Completion tip: Insert the drug names and if multiple drugs need consideration for exemption then, duplicate the section or questions for each drug.*

Is it me or do they ask every question twice?!?

1. ☐YES ☐NO	**Is there an IND issued for the drug used in this research?** If yes, STOP filling out this section and move to the Drug Information. Ensure the numbers are listed in IRES IRB.

3. ☐YES ☐NO	**Are you planning to submit this study to FDA for IND application?** If Yes, STOP filling out this section and move to the Drug Information. Ensure any correspondence from the FDA is uploaded in the Drugs section of the IRES IRB. Resources are available at Yale to help with IND support. Please, visit https://medicine.yale.edu/ycci/researchers/ors/indide/ for more information.

4. ☐YES ☐NO	**Has the FDA issued a determination that this study is exempt from IND requirements?** If yes, STOP filling out this section and move to the Drug Information. Ensure the FDA Letter is uploaded in the Drug page in IRES IRB.

- *Non-Sponsored research: FDA or the IRB may make the determinations. FDA determination trumps the IRB.*
- *The PI can also decide that an IND is warranted.*

Provide rationale that does not just reiterate criteria

5. ☐YES	**Do you believe the drug used in this research is exempt from IND requirements? Select the applicable exemption category below.** Please annotate the criteria below to provide justification, as needed, where it is not otherwise clear that 'the investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product,' for example.

This is often missed and will delay review if its needed and not provided.

A different colon mystery! It's missing!

Exempt Category 1	**The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are true (please check):** ☐The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☐The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☐The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☐The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☐The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.

Drugs Supplement

- An IND applies to the research - not just the drug. Once an IND is engaged - all drugs can be seen to be under that IND- with rare exception.
  - Completion tip: If you have an IND or are getting one, you do not need to complete a separate supplement for each drugs.

YALE Investigator initiated research:

- If you determine that an IND/IND is needed, or FDA or the IRB require it, then the Yale office for IND/IDE management will need to be utilized.
- All Yale IND/IDE holders must complete the supplement for 'Research Under an IND or IDE Held by a Yale Investigator'

Medical Devices Supplement

Many of the same tenants are true of devices and you will see similar questions in this supplement.

- If FDA has made the determination- tell us and skip the rest.

Completion tips:

➢ If multiple devices require consideration, the section can be duplicated.

➢ **Provide rationale for your selections**

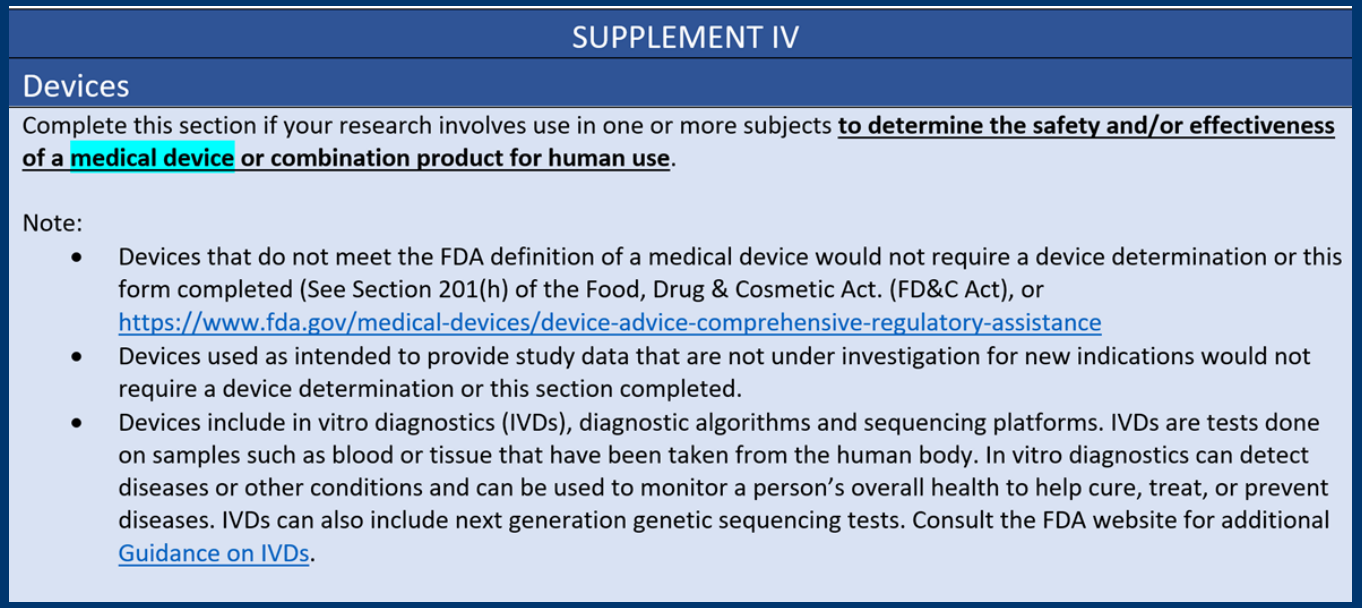
☐ YES ☐ NO	**Does, or will this device research operate under an IDE?** **If Yes, -** Enter the IDE number here and in the device section of IRES-IRB, upload supportive FDA documentation when available, and STOP completing this section.

3. ☐ YES ☐ NO	**Has the FDA assessed this device as exempt from the requirements of an IDE?** **If YES** – Check off '*Exempt from IDE Requirements*' in IRES IRB, upload the FDA correspondence that indicates IDE requirements do not apply to this research activity and STOP completing this section.

5. ☐ NO ☐ YES	**Do you or the sponsor believe the device is considered nonsignificant risk device?** **If YES** – Provide explanation below. **If NO** – Skip to question 6 below.
	Explain why the device does not meet the definition of a significant risk device (21 CFR 812.3(m)) by specifically addressing the criteria in the link.

Then why is our device supplement different?

- Many of the tenants of FDA device regulation are very different from drug and biologic regulation



SUPPLEMENT IV

Devices

Complete this section if your research involves use in one or more subjects **to determine the safety and/or effectiveness of a medical device or combination product for human use**.

Note:

- Devices that do not meet the FDA definition of a medical device would not require a device determination or this form completed (See Section 201(h) of the Food, Drug & Cosmetic Act. (FD&C Act), or https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance
- Devices used as intended to provide study data that are not under investigation for new indications would not require a device determination or this section completed.
- Devices include in vitro diagnostics (IVDs), diagnostic algorithms and sequencing platforms. IVDs are tests done on samples such as blood or tissue that have been taken from the human body. In vitro diagnostics can detect diseases or other conditions and can be used to monitor a person's overall health to help cure, treat, or prevent diseases. IVDs can also include next generation genetic sequencing tests. Consult the FDA website for additional Guidance on IVDs.

The applicability device regulation to **software, algorithms, AI , MMAs, SDA's** can be tricky to discern and is often the cause of the IRB asking you to complete the section so the IRB can be certain.

READ THE GREY BOX

In simple terms….

- Not all devices used in research are going to require an FDA regulation determination.
- The device used must first meet the FDA definition of a *medical* device.
- If the research is a clinical investigation of the FDA device (safety and effectiveness) – then **complete the supplement.**

Other Supplement Nuggets

Research with Tobacco Products

- FDA's definitions here are important: 'Tobacco product,' 'New tobacco product'
- 'Commercialized' does not mean FDA approved / not requiring ITP. We ask for this date because the regulation is partly based upon it.

Research with Radiation

- Investigational radiotracers must either be under IND, or if they meet certain criteria, under RDRC.
- **Review by Ancillary Committees:** *This supp very helpful to determine what other reviews are needed and how they start.*

Summary

- IRB Submission Form is meant to provide information NOT contained in the study protocol;
- Complete all REQUIRED sections and any of the applicable supplements;
- Pay attention to the help text and links provided.
- There is no need to duplicate information across sections or with the protocol,
- Definitely don't provide conflicting information.

Additional Resources

- **HRPP Website**
- **HRPP Policy and SOP Manual:** This document serves as the Yale HRPP Policy and Standard Operating Procedure Manual which serves as a guide for all components of the Human Research Protection Program, including the Institutional Review Board, Investigators and their Research Teams, and other members of the Research Community.
- **Investigator Manual:** The HRPP Investigator Manual provides detailed information on research preparation, IRB submission, and study team responsibilities.
- **Quick Guides**: step-by-step instructions for all system actions in IRES IRB Help Center;

Additional Resources

- Training on IRES IRB System (Yale IRBs)

- Training on IRES IRB System (external IRBs)

- Description: This on-line training session is designed for current and future PIs and coordinators of research studies under the purview of Yale IRBs. By the end of the session, the audience will gain an understanding of: - how to navigate the system; - how to submit protocols for initial and continuing reviews, - how to submit modifications and reportable new information, - where to find help.

Questions?

Questions? Contact HRPP@yale.edu
Yale HRPP Website
jennifer.reese@yale.edu
stacey.scirocco@yale.edu

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