



Notable Grand Rounds
of the
Michael & Marian Ilitch
Department of Surgery

Wayne State University
School of Medicine

Detroit, Michigan, USA

James H. Paxton, MD MBA

NAVIGATING THE
INSTITUTIONAL REVIEW BOARD

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About Notable Grand Rounds

These assembled papers are edited transcripts of didactic lectures given by mainly senior residents, but also some distinguished attending and guests, at the Grand Rounds of the Michael and Marian Ilitch Department of Surgery at the Wayne State University School of Medicine.

Every week, approximately 50 faculty attending surgeons and surgical residents meet to conduct postmortems on cases that did not go well. That “Mortality and Morbidity” conference is followed immediately by Grand Rounds.

This collection is not intended as a scholarly journal, but in a significant way it is a peer reviewed publication by virtue of the fact that every presentation is examined in great detail by those 50 or so surgeons.

It serves to honor the presenters for their effort, to potentially serve as first draft for an article for submission to a medical journal, to let residents and potential residents see the high standard achieved by their peers and expected of them, and by no means least, to contribute to better patient care.

David Edelman, MD
Program Director
The Detroit Medical Center

and

Professor of Surgery
Wayne State University School of Medicine

Navigating the Institutional Review Board

James H. Paxton, MD MBA
 Associate Professor of Emergency Medicine
 Wayne State University SOM

This paper is based on Dr. Paxton's Surgical Grand Rounds presentation on July 13, 2022 at the Wayne State University School of Medicine.

Audience

This paper is intended primarily (though not exclusively) for medical and surgical residents, who are required to do some type of scholarly activity as part of their residency training.

Objectives

The IRB is traditionally seen as a daunting hurdle to initiating research. In large part, that may be because researchers understand the mechanics—the process—but not the mindset of the IRB. The mechanics are well-documented, but the mentality of the IRB committee members in reviewing proposals may not be as clear to the novice researcher. Understanding the IRB perspective may help researchers to successfully navigate the IRB review process.

Specifically, the objectives of this paper are to:

1. Outline major **regulatory policies** developed in clinical research
2. Describe **key concepts** involved in the ethical conduct of research
3. Discuss the **role of the IRB** in regulating human subjects research
4. Identify key **IRB priorities** in their review of research protocols

5. Describe the **process** of IRB submission, including common **pitfalls** to successful approval of a clinical research protocol
6. Introduce the novice surgical researcher to valuable WSU IRB **personnel and resources** that they will need to succeed

Historical Precedents: Regulatory Policies and Context for the IRB Mindset

From the public's perspective, medical researchers may seem to be ethically deviant, or even downright evil! Historically, medical researchers have done highly immoral things (by today's standards) behind closed doors. This is the burden that modern researchers have inherited from our predecessors – whether we like it or not.

In part, the Institutional Review Board (IRB) exists to allay these public concerns. They are the “ethics police” for medical research, and are our allies in the effort to undo the damage that our forebears have done to our reputations. They want to help—but sometimes that “help” seems more like a burden.

It is true that medical research has a poor ethical track record. In the Middle Ages, physicians dissected people such as convicts and followers of proscribed religions while they were still alive

(i.e., vivisection). They would rob graves and use the corpses for teaching anatomy to med students. Up until only about 150 years ago, “scientists” conducted all manner of research on people without asking their permission or even telling them what they were doing.

The Nuremberg Code

During World War II, Nazi medical researchers experimented on prisoners of war and especially on Jewish people, exposing them to nerve gas, freezing them, doing all manner of terrible things. One defense offered by these “scientists” at the post-war Nuremberg trials was that there were no secular laws prohibiting such research, which was actually true at the time.

These atrocities led to the publication of the *Nuremberg Code* in 1947, which made ten recommendations:

1. Required is the **voluntary, well-informed, understanding consent** of the human subject in a full legal capacity.
2. The experiment should aim at positive results for society that **cannot be procured in some other way**.
3. It should be based on previous knowledge (like, an expectation derived from animal experiments) that **justifies the experiment**.
4. The experiment should be set up in a way that avoids **unnecessary physical and mental suffering** and injuries.
5. It should not be conducted when there is any reason to believe that it **implies a risk of death or disabling injury**.

6. The **risks** of the experiment should be in proportion to (that is, not exceed) the expected humanitarian **benefits**.
7. Preparations and facilities must be provided that adequately **protect the subjects** against the experiment’s risks.
8. The staff who conduct or take part in the experiment must be fully **trained and scientifically-qualified**.
9. The human subjects must be free to immediately **quit** the experiment at any point when they feel physically or mentally unable to go on.
10. The medical staff must **stop** the experiment at any point when they observe that continuation would be dangerous.

The Declarations of Geneva and Helsinki

The Nuremberg Code was followed a year later by the *Declaration of Geneva* and in 1964 by the *Declaration of Helsinki*, the first significant effort by the medical community to self-regulate research. The Helsinki Declaration was adopted by the World Medical Association that same year. It:

- Permitted **proxy** consent (by a responsible relative)
- Honored **patient’s rights** over society’s interests
- Recommended oversight by “**independent committees**” (e.g., IRBs)
- Required that the **consent of minors** in research be obtained when possible¹

The *Declaration of Geneva* produced a statement which built upon the *Hippocratic Oath*. It was for all physicians, not just researchers, setting out their ethical responsibilities (Figure 1).

¹ Asking a five-year-old for consent then poking and doing all kinds of mean things to them when they don’t really understand what’s going on is of course of grave concern. Even parents who give proxy permission may not explain it well to the child. This requirement seeks to protect minors by requiring some type of assent from the child to engage in research, even if they are too young to provide truly informed consent. Every effort must be made to explain to the child, in terms that s/he can understand, what the researchers are going to do and why.

DECLARATION OF GENEVA

At the time of being admitted as a member of the medical profession:

I SOLEMNLY PLEDGE

to consecrate my life to the service of humanity

I WILL GIVE

to my teachers the respect and gratitude that is their due

I WILL PRACTISE

my profession with conscience and dignity

THE HEALTH OF MY PATIENT

will be my first consideration

I WILL RESPECT

the secrets that are confided in me, even after the patient has died

I WILL MAINTAIN

by all the means in my power, the honour and the noble traditions of the medical profession

MY COLLEAGUES

will be my sisters and brothers

I WILL NOT PERMIT

considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient

I WILL MAINTAIN

the utmost respect for human life

I WILL NOT USE

my medical knowledge to violate human rights and civil liberties, even under threat

I MAKE THESE PROMISES

solemnly, freely and upon my honour

Fig. 1. Declaration of Geneva

The Birth of the IRB

The *Declaration of Helsinki* recommendation of oversight by independent committees led to the birth of the Institutional Review Board in America. Unfortunately, increased regulation of medical research in this country has not prevented unethical research from happening. In just the past 50 years, the US government itself has au-

thorized research such as intentionally infecting subjects with hepatitis C or syphilis or yellow fever just to see what would happen, while withholding treatment. In the Tuskegee syphilis study, for example, which ran for 40 years in the United States, penicillin was withheld from syphilitic patients just to see what would happen to them.

The National Research Act and the Belmont Report

It is understandable that some citizens don't trust researchers and that collectively, researchers still need to get past a disreputable historical past. After conducting hearings on unethical research involving human subjects (including the Tuskegee study) Congress passed the *National Research Act* in 1973, which President Nixon signed into law in 1974. It authorized federal agencies (e.g., NIH, FDA) to develop regulations governing human subjects research and required institutions to form IRBs to review and oversee research involving human subjects.

The *Belmont Report*, developed at the Smithsonian's Belmont Center in Elkridge, MD, was promulgated by the National Commission for Protection of Human Subjects in 1979. It defines:

- The boundaries between biomedical and behavioral **research** and the accepted and **routine practice** of medicine. Patients often don't understand whether their treatment is part of research or is specific to them, or is just standard practice.
- Role of assessment of **risk-benefit criteria** in the determination of the appropriateness of research involving human subjects.
- Appropriate **guidelines for the selection** of human subjects for participation in such research.
- The nature and definition of **informed consent** in various research settings.

The Code of Federal Regulations (CFR)

The Code of Federal Regulations (CFR) Title 45 Part 46: "Protection of Human Subjects," promulgated by the US Department of Health and Human Services (HHS), sets out the bureaucratic rules that IRBs must follow, especially pertaining to organizational and enforcement matters, record-keeping, documentation of informed con-

sent, interpreting risk / benefit ratios, etc. But it does not touch upon ethical issues except to say that IRBs will review protocols to make sure that they are ethical.

Ethical matters are really left to the individual local IRBs, to determine whether research protocols are ethical and moral.

The Common Rule

The Common Rule, also known as "The Federal Policy for the Protection of Human Subjects," is part of a CFR regulation first published in 1981 and revised in 2018. It is "common" because it provides governance for all US federal agencies engaging in human subjects research, including:

- Requirements for assuring compliance by research institutions.
- Requirements for researchers' obtaining and documenting informed consent.
- Requirements for IRB membership, function, operations, review of research, and record keeping.

The above bullets constitute the primary policy ("Subpart A") of the Common Rule. "Subpart B" contains additional protections for pregnant women, *in-vitro* fertilization, and fetuses; "Subpart C" has additional protections for prisoners; and "Subpart D" has additional protections for children.

HIPAA

The *Health Insurance Portability and Accountability Act* (HIPAA) of 1996 consists of a Privacy Rule ("Standards for Privacy of Individually Identifiable Health Information") which establishes national standards for the protection of certain health information, and a Security Rule ("Security Standards for the Protection of Electronic Protected Health Information") which establishes

standards for protecting certain health information held or transferred in electronic form.

HIPAA sets limits to restrictions concerning pre-existing conditions and provides for national provider identifier (NPI) numbers. It also regulates the use of medical history and billing or payment information by requiring disclosure of the minimal amount of information needed.

The Institutional Review Board

The main job of the IRB is to protect research subjects, generally patients in the setting of medical research. The IRB committees are made up of researchers, clinicians, and others including ordinary citizens. The *only* reason that IRBs exist is to make sure that research subjects are safe. Of course, the IRB members may have opinions about the feasibility, validity, or other aspects of the research protocols they are asked to review but such aspects are not their primary consideration.

They might reject a project because they don't want subjects wasting their time on something that just is not going to work, but in that case they are still looking out first and foremost for the safety of research subjects. The IRB is not focused primarily on reviewing or criticizing the academic quality of a protocol; their focus is on the risks and benefits of the proposed research to the subject.

The IRB assesses a study's risks and benefits, how it will be monitored, the strategy for recruitment of subjects, the process for obtaining informed consent, and how privacy and confidentiality will be maintained.

Principles of Ethical Research

The basic principles of ethical research are centered on four concepts: Beneficence, Nonmaleficence, Autonomy, and Justice. The IRB looks for

the presence of these elements in all submissions.

1. *Beneficence* is providing benefit to others, with the goal of maximizing the benefits to participants and society, although the benefit to participants may be indirect (by benefiting society as a whole, future patients, and family members, etc.) Physicians should not engage in research that does not provide a benefit to participants or to society.

2. *Nonmaleficence* sounds like it should be the same thing, but it is not. It harkens back to the Hippocratic Oath's *Primum non nocere* (First do no harm). It means minimizing the risk, if there is any, to participants. Research can't exist without *some* risk, including physical and mental/emotional harm, monetary costs, wasted time, and loss of privacy if research data are misplaced or stolen. However, risks should be fully disclosed to subjects at the time of obtaining informed consent for study enrollment. Subjects should understand the risks of involvement in the research study, and those risks should be minimized.

3. *Autonomy* means the capability to deliberate on personal goals and act under the direction of such deliberation, according to the *Belmont Report*. Participants must be able to make decisions about whether to be involved in the research at all and what will happen to them if they do. That requires full disclosure of information to the participant and the absence of any coercion. Participation *must* be voluntary, and to prove this informed consent must be documented.

Prisoners, minors, people with mental disabilities may not have a full understanding of the research protocol and may not be capable of weighing the risks and benefits, the potential adverse effects of the protocol, and whether alternatives are available. It is acceptable for legally

authorized representatives (LARs) to make decisions or sign paperwork for subjects as long they are people that the patient would want to make those decisions for them. In the case of minors, it is still necessary to try to explain to them what is going to happen to them by obtaining their assent to be involved in the research study.

4. *Justice* is a relatively abstract concept, but in the medical research context it relates to subject selection: Who's going to be involved in the research? Who will bear the costs? Will vulnerable and under-represented groups have equal access to study participation? Will standard-of-care medical treatment be provided to those who decline to be enrolled in the study?

The IRB's job is primarily to protect vulnerable people from risk, but it has a secondary responsibility to advocate for their equitable inclusion in studies that might benefit them directly or indirectly—not just the people researchers might mainly be interested in (say, African Americans, or Catholics, or people who live above the Arctic Circle) unless adequate justification for exclusivity is provided.

What Requires IRB Review: The Regulations and How They Apply to Medical Research

The IRB reviews human participant research—defined as a “systematic investigation involving information about and interaction or intervention with living individuals”—that is designed to contribute to generalizable knowledge.

What is not human subjects research? The IRB does not need to review:

- *Case Reports* (or *Case Series* of 3 or less subjects). It may, however, depending on the case, provide a letter addressed to a journal editor confirming that ethical guidelines were

followed in a particular case being submitted for publication.

- *Course-Related Activities*
- *Decedent Activities* (e.g., exclusively cadaver studies)
- *Journalism / Documentary / Oral History*
- *Quality Improvement / Program Evaluation*: It is sometimes hard to distinguish whether a protocol is research or quality improvement. The IRB is always happy to advise if there is any uncertainty.
- *Public-Use Datasets*: Information that may have been private but is now widely available in the public domain is no longer private so neither the IRB nor anyone else has a responsibility, not to mention the power, to protect it.
- *Public Health Surveillance*: If there is any doubt whether a public health initiative counts as research, the IRB should be asked to adjudicate.
- *De-identified Data or Biospecimens*

For more information concerning human subjects participation, visit <https://prezi.com/v/ymjvqms-bxetr/irb-on-demand-does-my-study-need-irb-review-part-1/> and

<https://prezi.com/v/5e8wqnppubw/irb-on-demand-video-slides-only-does-my-study-need-irb-review-part-two/>. Wayne State University researchers may also email

IRBQuestions@wayne.edu and access the Human Subjects Participation Tool at https://research.wayne.edu/irb/docs/hpr_determination_tool_revised_11_2021.pdf

Waiver of Consent (WoC)

In studies involving data from hundreds or thousands of participants from whom informed consent would be impossible to obtain, the IRB can grant a 3-year “Type 2” waiver. Such studies usually take the form of retrospective chart re-

views. Journals often require IRB approval in advance of publication of such studies.

If research is intended to produce generalizable conclusions, it is preferable to obtain determination of “exempt” status prior to data collection.

Any prospective study of (say) an intervention involving people with a certain condition (for example, people who have a history of appendectomy) will require consent for the intervention itself but chart review to identify potential participants may be given a 1-year “Type 1” waiver.

Composition of an IRB

An IRB committee typically includes about 15 people whose job it is to decide if a study meets regulatory and ethical requirements. Some are researchers, some are physicians, some are nurses, some are pharmacists, some are lay members of the community. The latter in particular may not speak medical jargon, which should therefore be minimized in IRB submissions. Investigators should know their audience, and plan to submit a proposal that will be intelligible to the entire IRB committee. A high-school level of English is likely to be processed more smoothly and with less frustration than a submission requiring an MD degree to understand. A frustrated reviewer will have a harder time approving the study.

Of course, many IRB members may understand medical jargon, but all IRB members need to understand the submission sufficient to apply the four concepts mentioned earlier and be able to fulfill their duty to protect participants.

For each protocol submitted, the IRB Chair will generally designate one member to be the primary reviewer and another to serve as a secondary reviewer. The primary reviewer will present a summary of the protocol to the full

Board and point out any issues or problems they have discovered. The secondary reviewer may add his or her own comments.

If there are concerns that require additional consideration by the whole board, then approval may be denied or postponed until the next meeting of the IRB. Since IRBs typically meet once per month, the researcher’s goal should therefore be to minimize confusion at the time of the first submission, to avoid potential delays relating to re-submission.

IRB members and staff pay particular attention to the following, therefore the researcher should too:

- Conflicts of interest
- Research Staff credentials and training
- Protocol / Proposal
- Potential for coercion
- Risk / Benefit analysis
- Regulatory compliance (HIPAA: when health information is involved)
- Application(s)
- Consent forms (13+ required elements)
- Any other documents related to the research that participants will see

The IRB is looking for conflicts of interest, and also looks at the researcher’s credentials (i.e., qualifications and experience). The potential of coercion of vulnerable participants such as pregnant women, prisoners, people with psychiatric illness will be scrutinized. The IRB will look for potential risks and benefits, for the individual or for society, so it is important to note these clearly in the protocol and in the consent forms.

Things to Consider Before Preparing IRB Submission

Receiving IRB approval can take several weeks at best, and months if there are issues with it, so

researchers should build enough time into their timeline to prepare the IRB submission and obtain IRB approval with enough time remaining to conduct the research and write the manuscript.

At Wayne State University, the entire study team—Principal Investigators (PIs), key personnel, and authorized signatories—must have completed WSU’s Collaborative Institutional Training Initiative (CITI) training modules in order to understand and act in accordance with the requirements of the regulations pertaining to the protection of human participants in research. Once CITI has been completed, a Basic Course in Human Subjects Research must be renewed every three years.

A detailed research protocol/proposal with references is required, describing in detail the following processes:

- Recruiting and consenting participants
- De-identification of data
- Secure storage of research data and research related documents (consent form, completed surveys, etc.)
- Secure destruction of research data and research related documents when study is complete.

Minimal Risk

Research protocols that put participants at greater risk than they would encounter in everyday life are reviewed by and voted on by a full convened board. If the protocol involves only minimal risk, then one experienced IRB voting member may conduct the risk assessment. A low risk protocol may be eligible for expedited review. A “no-risk” protocol may qualify for exemption from review. However, the determination of whether a proposal is exempt from IRB review should be made by the IRB – not by the investigator.

IRB Committees

IRBs may have various committees, such as medical adult, medical pediatric, and social / behavioral / educational (as with Wayne State). Applicants may request a specific committee to review their protocol, but the IRB will determine which committee reviews each protocol.

Tips for a Smooth Review

Applicants should carefully study their institution’s IRB website, and ensure that they have included all the required documents and that the documents are internally consistent. In the event of comments and questions from the IRB, investigators should remember that while the researcher’s focus is on the research, the IRB’s focus is on protecting research subjects. The researcher’s protocol and any responses to the IRB’s comments would do well to reflect this understanding of the IRB’s perspective.

Researchers should not propose anything that they would not be comfortable with as participants themselves. They should be detailed in their responses to the IRB’s questions about consent and data collection, protection, and storage. They should also identify key differences in seemingly redundant questions to understand what the IRB is looking for.

Not least, they should not only respond promptly to communications from the IRB but also be proactive in asking questions of the IRB. *The IRB wants to help the researcher get through the review process.*

IRB Applications

At Wayne State University, researchers submit applications, along with any required forms, via an electronic system called *e-Protocol*. Communications with the IRB also take place through *e-Protocol*. Information about *e-Protocol* is avail-

able at their website (<https://research.wayne.edu/eprotocol>).

The components of an IRB Application are generally:

- Protocol Summary Form (PSF)
- HIPAA Summary Form
- Participant Consent / Assent Forms
- Appendices A-L (includes details of any devices, drugs, etc. that are to be used)
- Full Protocol
- Supplementary Documents

Approvals

Types of IRB approval include:

1. Exempt – No IRB Approval or Review Needed. However, the researcher must still submit a form to the IRB for review. The IRB will issue a letter of exemption if the study is found to be exempt. A study is exempt if ALL of the following are true:
 - The study is not intended to yield generalizable knowledge
 - No intervention or interaction with patient is involved
 - No PHI is used
 - Not “private” information
 - The study is not to test the safety or efficacy of a drug/device
2. Expedited – Continuous Review (No Deadline). This type of approval is usually for things more risky than a simple chart review, such as an observational study that involves collecting blood samples from patients. It can be expedited because there is no risky intervention involved. Expedited cases may be reviewed by an outside reviewer and decisions are usually given within a month.

3. Full Board Review – Monthly Reviews (FB) – is generally reserved for studies with more than minimal risk involved. Most research that's not chart review, or observational, or just simple blood collection will require full board review at a regularly-scheduled IRB meeting.
4. Humanitarian Use Device (HUD) – FB: The IRB may approve studies to use a device that is not FDA cleared for the researcher's intended use in the following instances:
 - The market is too small for FDA clearance to be feasible
 - The use can be shown to be compassionate

Amendments to a Submission

The IRB recognizes that research is dynamic. For example, the originally anticipated number of participants may need to be increased, or additional researchers may be added. Such changes still have to be approved by the IRB, via signed forms affirming no conflicts; etc.

If a study needs to be extended beyond the initial approval period, a continuation form must be submitted. If it is to become a multiple site study, a coordinating center application is required for the site that will act as the study coordinating site.

Finally, a closure form tells the IRB that a study has been completed.

Applicants should always keep a backup of their submission and use “track changes” in their word processor when amending and re-submitting any documents so that the reviewer(s) can easily see the changes made since they last reviewed the document. Reviewers can't be expected to memorize every submission and it takes a great

deal of (frustrating) work to manually compare two versions of a submission.

Pitfalls

Pitfalls exist in relation to: standard operating procedures (SOPs); submission elements; forms, styles, and grammar; safety and risk; and obtaining informed consent.

1. SOPs: May contain inadequate description of the screening and consent process: Was a HIPAA waiver obtained? Was the justification adequate? Inclusion and exclusion criteria may be lacking or unclear, especially with respect to vulnerable populations. The plan for data storage and use may lack details such as who has access, what is the location of the data, what are the coding procedures, and privacy / confidentiality safeguards—password protection, authentication, a firewall?

2. Submission Elements. Common pitfalls are:

- Incomplete submissions
- Not responding to IRB queries
- Failure to list / add all Key Personnel
- Inappropriate key personnel titles (e.g., Chief Investigator; Co-PI vs. Co-I)
- Missing signatures from Key Personnel / Chair
- Cutting / pasting from other documents (i.e., inappropriate references)
- Missed deadline
- Failure to complete required training (e.g., CITI)

3. Forms, Style, and Grammar: Poor English is hard to read and leads to frustration. No researcher should want their overworked, under-appreciated, and unpaid reviewer to be frustrated by typos and bad grammar.

4. Safety and Risk: It is important to be clear about any risk involved in the data collection or the intervention. Clear distinctions should be made in both the protocol and the informed consent document between what is “standard of care” management (not research) and what is considered to be a research procedure.

“In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.... (45 CFR 46.111(a)(2)).”

Contingencies (should harm occur) must also be addressed — Who should be informed, what should they do? And what will you do if participants drop out? Will their data be kept? Will there be follow up?

Failure to address these issues can delay the application and derail the proposed research.

5. Consent: Is informed consent required for the study?

- What will happen if a patient refuses to participate?
- Accurate description of direct benefits to subject?
- Compensation listed as a benefit to inclusion
- Failure to include all appropriate risks
- Inadequate time to review consent document
- Any changes made to the Informed Consent form needs to be approved by the IRB

Legally Authorized Representative (LAR)

- In prospective research, there may be a need to involve surrogate consenting, such as for

patients in cardiac arrest or delirious or demented or have other medical problems that prevent them from being able to provide informed consent. A LAR may give consent, and increasingly many do so remotely through electronic means.

The Bottom Line

The key to successful passage through the IRB process is not to wait until frustration brings the study to a halt. Talk to the IRB. At Wayne State, see the contacts show in Figure 2 below. Email them. Email me! (james.paxton@wayne.edu). I'm glad to help.

* * *

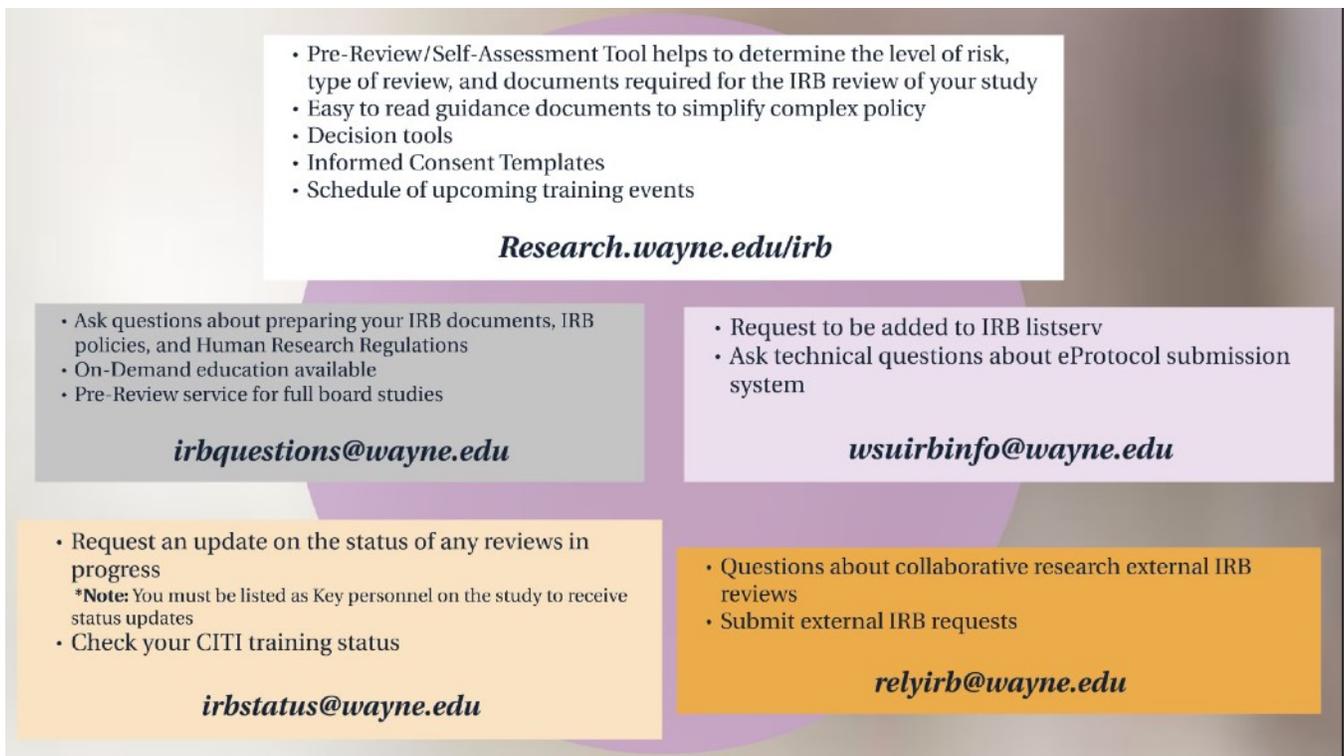


Fig. 2. IRB Contacts