IRB Determinations 101: What Does It All Mean

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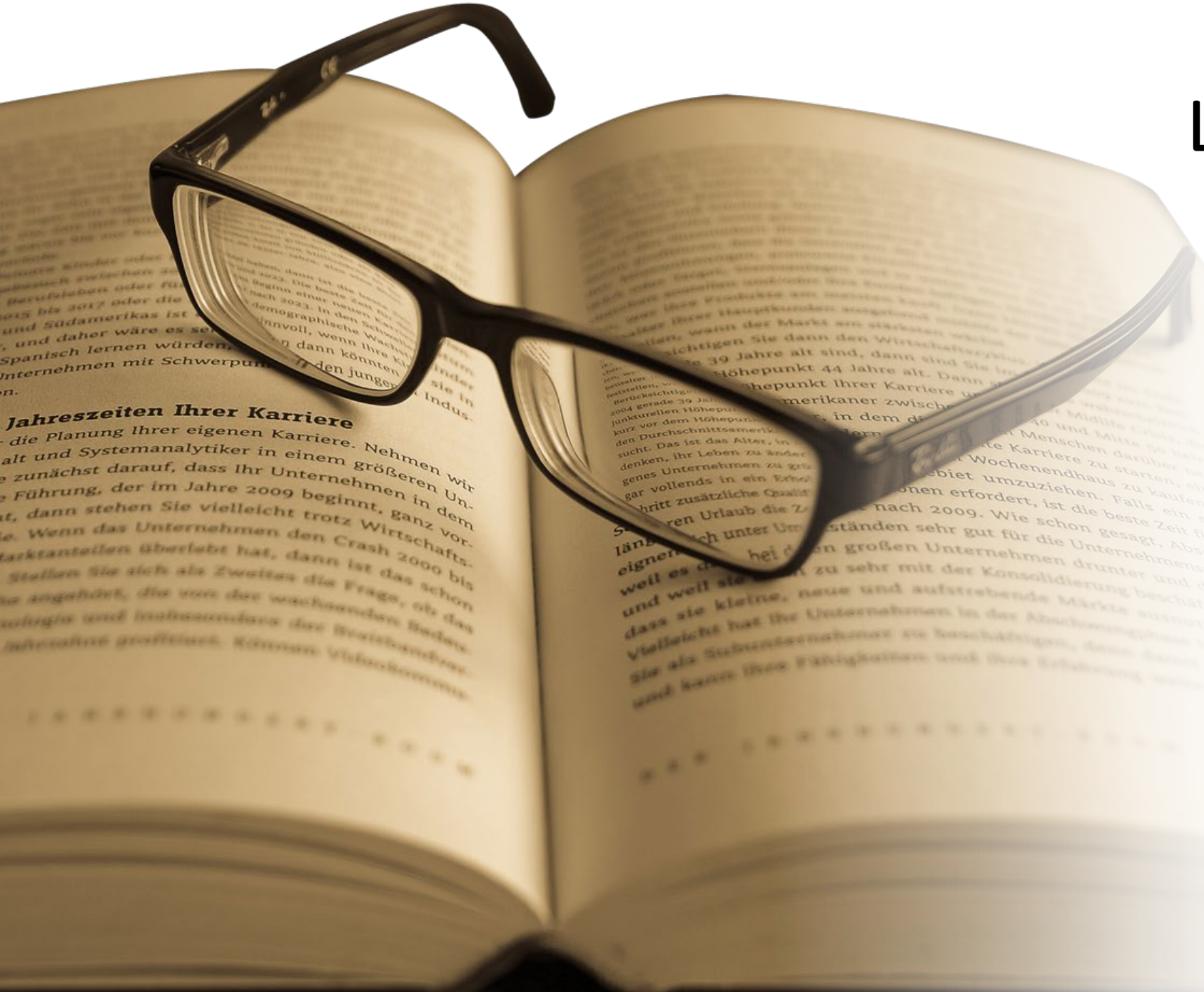


Learning Objectives

- Understand the basic order and process of IRB determinations
- Recognize activities that meet the federal definition of research
- Understand risk determinations and their basis in federal regulations
- Identify categories of exempt and expedited review
- Describe the basic types of IRB submissions and their timing within the life cycle of a human subject research study

Your Friendly Neighborhood IRB

- The Institutional Review Board is charged reviewing research involving human subjects to ensure that the rights, welfare, and privacy of human subjects in research are protected.
- Follow written procedures and where applicable review research according to Title 45 Code of Federal Regulations Part 46 (Common Rule) and Title 21 Code of Federal Regulations Parts 50 and 56 (FDA human subject regulations)
- The IRB does not have the authority to retrospectively review a protocol or provide retroactive approval.
- We are available for questions about your research and its review. Call us, we can help you! X23535

Basic Types of Submissions

Initial submission

When you are planning a research project

If you think a project may not be human subjects research and want a determination to document this

Before data collection and analysis NOT after the work is done

Continuing review

Not required for most minimal risk research

Required annually for FDA research regardless of risk

Not less than once per year for research considered greater than "*minimal risk*"

Modification

Changes to research that has been reviewed

Report of New Information

Annual safety reviews

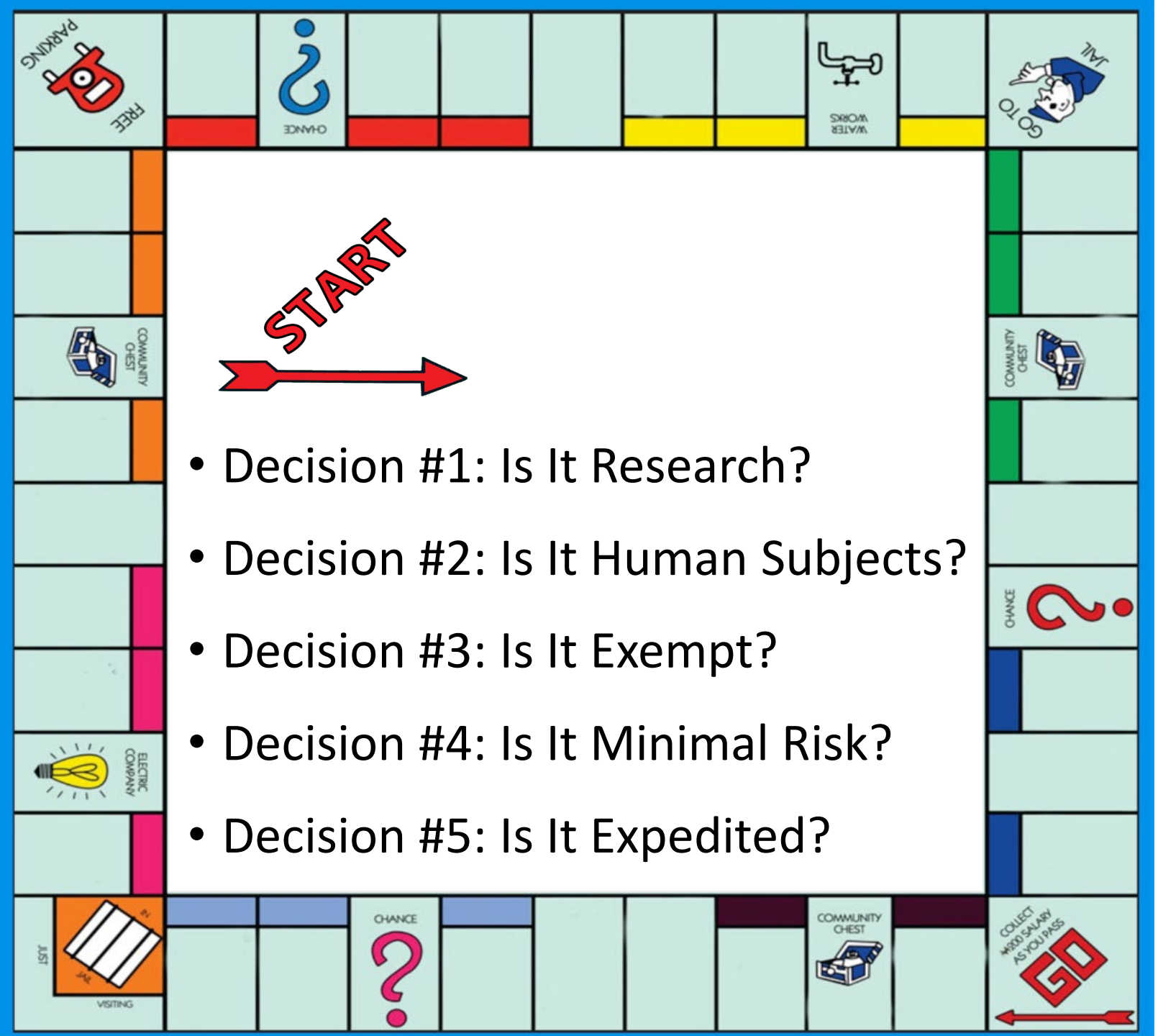
DSMB reports

Protocol deviations

Adverse events

Initial Submissions

- How are studies evaluated when thy are first submitted?
- Which agency regulations apply?
  - OHRP Common Rule – applies to any federally funded research and provides a broad framework for evaluating human subject research
  - FDA – applies any time a test article is in use that would be subject to FDA regulation



- Decision #1: Is It Research?
- Decision #2: Is It Human Subjects?
- Decision #3: Is It Exempt?
- Decision #4: Is It Minimal Risk?
- Decision #5: Is It Expedited?

MONOPOLY

Framework for Making Determinations

Not Minimal Risk?

Go Straight to
Full Board Review

What is Research? ….according to Federal Regulations

- Can be very challenging to determine
- Activities that meet the federal definition of research involving human subject are subject to IRB oversight
- IRBs do not oversee activities that are classified as something other than human subjects research (HSR) based on the federal definition

What is Research?

According to the Common Rule 45 CFR 46.102(d)

*a **systematic** investigation, including research development, testing and evaluation, designed to develop or contribute to **generalizable** knowledge*

What is Research?

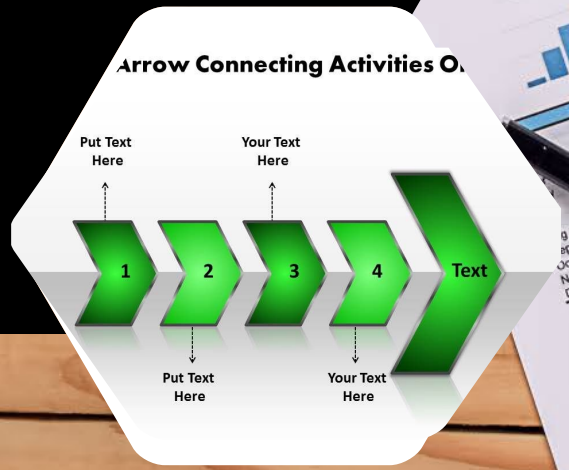
According to the FDA 21 CFR 56.102(c)

clinical investigation is *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 FDA, or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit*

The terms *research, clinical research, clinical study, study,* and *clinical investigation* are deemed to be synonymous for purposes of this part.

Does the activity involve a *systematic* investigation?

- Is there a **methodical** approach?
- Does it involve a hypothesis, research question, and a **plan** to collect and analyze data?



Is the activity designed to develop or contribute to *generalizable* knowledge?

- The systematic investigation adds information and contributes to **generalizable** knowledge in the field.
- Some types of research reports are not typically considered generalizable such as case reports or individual n-of-1 studies.
- Research that is specific to a time, place, and/or situation might not be considered to contribute to generalizable knowledge.

Categories of Activities Deemed Not to Be Research

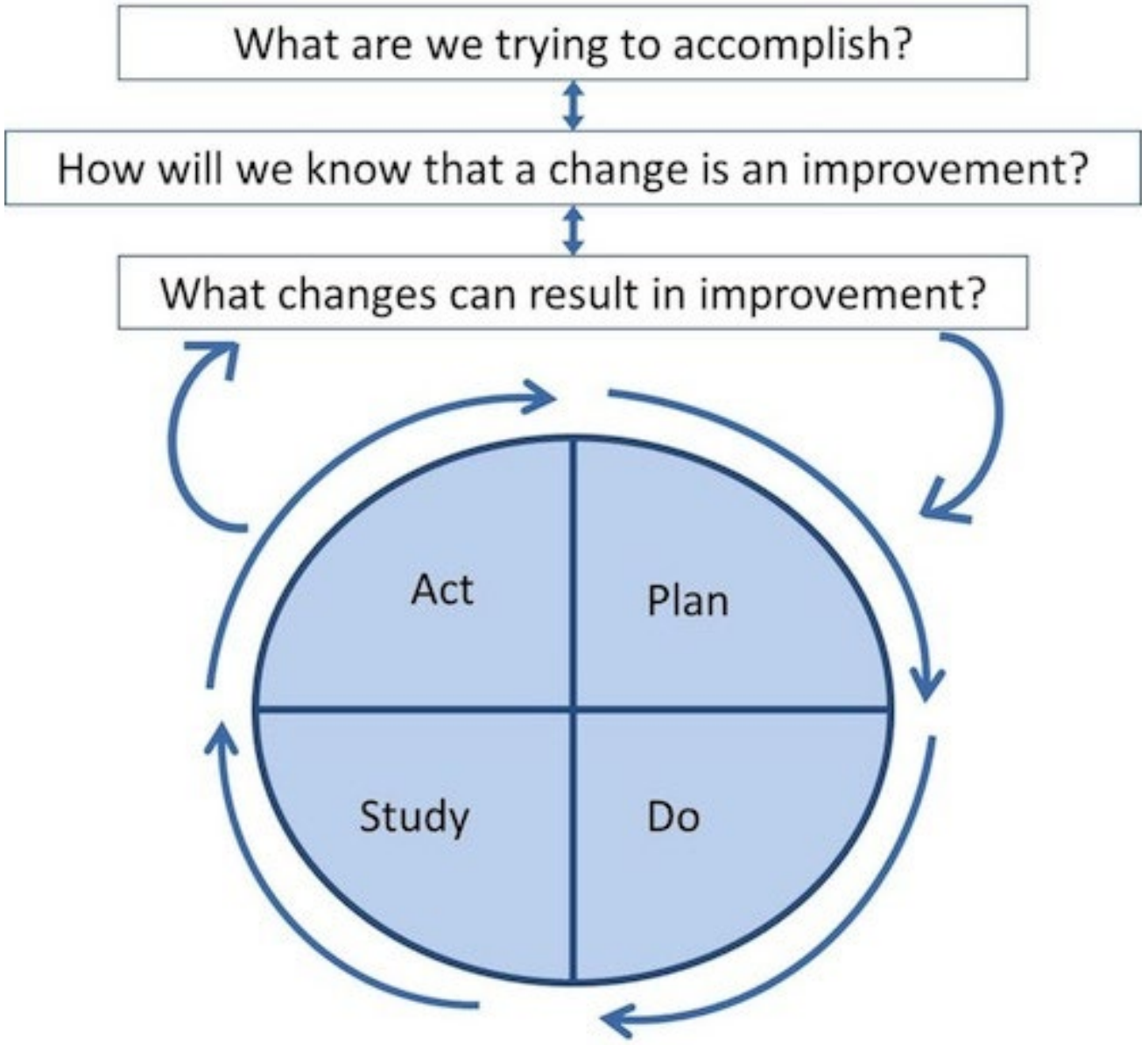
- Scholarly and journalistic activities that focus on information specifically about certain individuals.
- Certain public health surveillance activities.
- Certain activities solely for criminal justice or criminal investigative purposes.
- Certain operational activities in support of national security missions.

Does publishing mean its research?

- Whether or how an investigator shares results with the scientific community is not the deciding factor for whether the activity was designed to develop or contribute to generalizable knowledge.
- Caveat: If you want to publish it, submit to the IRB for a determination as most journals will ask.

What's the Difference between QA/QI and Research?

- QA/QI projects identify specific services, protocols, practices, processes, or outcomes for improvement. The main goal is to improve patient care.
- Sometimes, QA/QI activities are research.
- In those cases, IRB review is necessary.
- If you're unsure, call or email us x23535 or irb@ochsner.org



Is it likely to be considered Research, QI, or Both?

	Human Subjects Research	Quality Improvement
Purpose	designed to develop or contribute to generalizable knowledge	designed to implement knowledge, assess a process or program as judged by established/accepted standards
Starting Point	knowledge-seeking is independent of routine care and intended to answer a question or test a hypothesis	knowledge-seeking is integral to ongoing management system for delivering health care
Design	follows a rigid protocol that remains unchanged throughout the research	adaptive, iterative design
Benefits	might or might not benefit current subjects; intended to benefit future patients	directly benefits a process, system or program; might or might not benefit patients
Risks	may put subjects at risk	does not increase risk to patients, with exception of possible patients' privacy or confidentiality of data
Participant Obligation	no obligation of individuals to participate	responsibility to participate as component of care
Endpoint	answer a research question	improve a program, process or system
Analysis	statistically prove or disprove hypothesis	compare program, process or system to established standards
Adoption of Results	little urgency to disseminate results quickly	results rapidly adopted into local care delivery
Publication	investigator obliged to share results	QI practitioners encouraged to share systematic reporting of insights

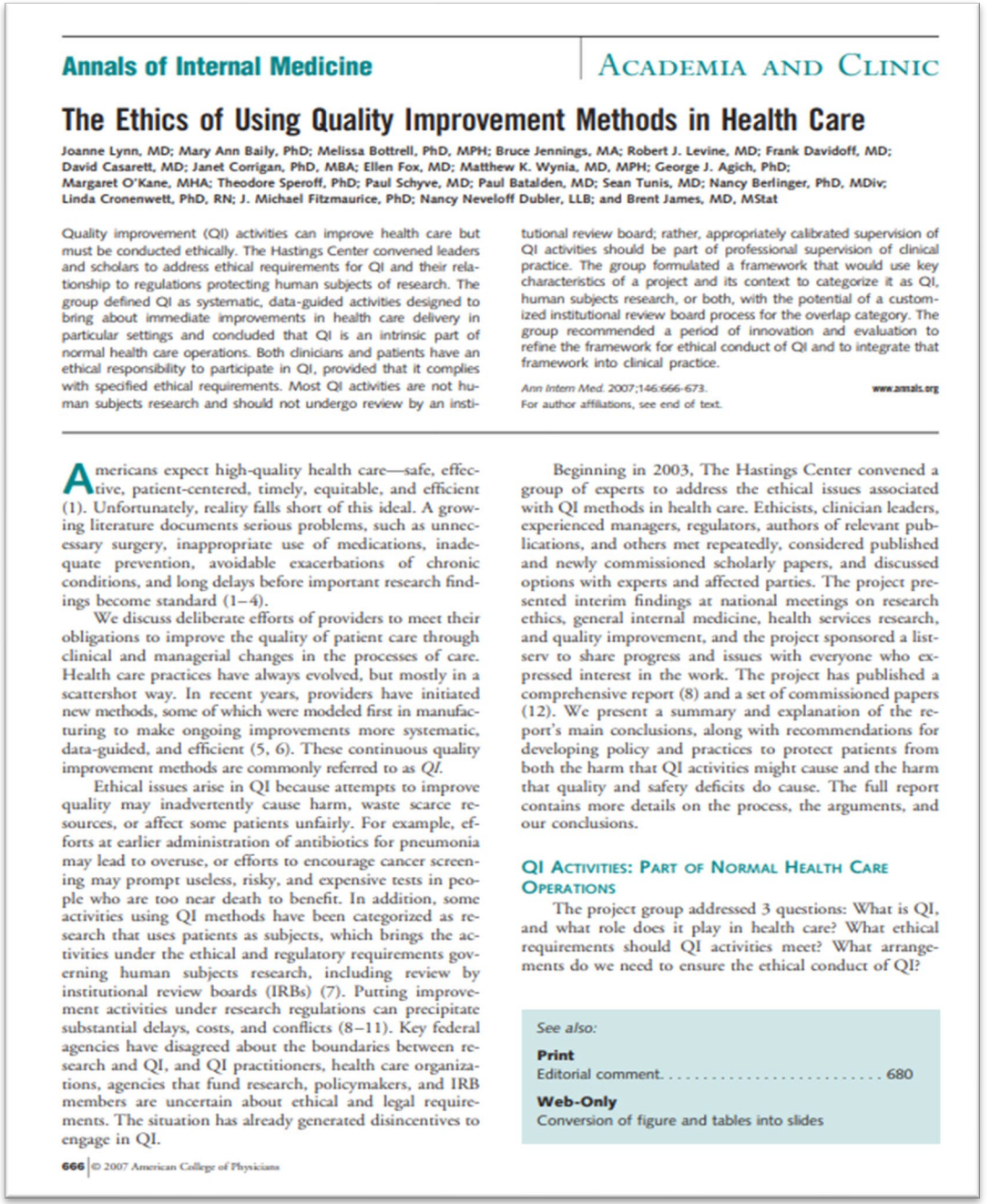
When is IRB approval needed for QI activities?

IRB approval may be required when the activity involves some of the following characteristics:

- seeks to develop new knowledge or validate new treatments rather than to assess the implementation of existing knowledge;
- when the methodology employs specific characteristics of experimental research design, for example, randomization;
- when the protocol is fixed with a rigid goal, methodology, population, time period, etc.;
- when the funding for the activity comes from the outside organizations such as the NIH or those with a commercial interest in the results;
- when there will be a significant delay in the implementation of results;
- when the risks from the intervention to participants are greater than minimal

Resources & Reference

- *The Ethics of Using Quality Improvements in Health Care* contains a detailed discussion of the differences between QI and research
- *The Common Rule and Continuous Improvement in Health Care* a discussion paper sponsored by the Institute of Medicine discusses the interactions and overlap between QI and research.
- Vogelsang J. *Quantitative research versus quality assurance, quality improvement, total quality management, and continuous quality improvement*.
- Casarett et al. *Determining when quality improvement initiatives should be considered research: proposed criteria and potential implications*.
- Grady C. *Quality improvement and ethical oversight*.
- Miller and Emanuel. *Quality-improvement research and informed consent*.



Annals of Internal Medicine | ACADEMIA AND CLINIC

The Ethics of Using Quality Improvement Methods in Health Care

Joanne Lynn, MD; Mary Ann Baily, PhD; Melissa Bottrell, PhD, MPH; Bruce Jennings, MA; Robert J. Levine, MD; Frank Davidoff, MD; David Casarett, MD; Janet Corrigan, PhD, MBA; Ellen Fox, MD; Matthew K. Wynia, MD, MPH; George J. Agich, PhD; Margaret O'Kane, MHA; Theodore Speroff, PhD; Paul Schyve, MD; Paul Batalden, MD; Sean Tunis, MD; Nancy Berlinger, PhD, MDiv; Linda Cronenwett, PhD, RN; J. Michael Fitzmaurice, PhD; Nancy Neveloff Dubler, LLB; and Brent James, MD, MStat

Quality improvement (QI) activities can improve health care but must be conducted ethically. The Hastings Center convened leaders and scholars to address ethical requirements for QI and their relationship to regulations protecting human subjects of research. The group defined QI as systematic, data-guided activities designed to bring about immediate improvements in health care delivery in particular settings and concluded that QI is an intrinsic part of normal health care operations. Both clinicians and patients have an ethical responsibility to participate in QI, provided that it complies with specified ethical requirements. Most QI activities are not human subjects research and should not undergo review by an institutional review board; rather, appropriately calibrated supervision of QI activities should be part of professional supervision of clinical practice. The group formulated a framework that would use key characteristics of a project and its context to categorize it as QI, human subjects research, or both, with the potential of a customized institutional review board process for the overlap category. The group recommended a period of innovation and evaluation to refine the framework for ethical conduct of QI and to integrate that framework into clinical practice.

Ann Intern Med. 2007;146:666-673. www.annals.org
For author affiliations, see end of text.

Americans expect high-quality health care—safe, effective, patient-centered, timely, equitable, and efficient (1). Unfortunately, reality falls short of this ideal. A growing literature documents serious problems, such as unnecessary surgery, inappropriate use of medications, inadequate prevention, avoidable exacerbations of chronic conditions, and long delays before important research findings become standard (1–4).

We discuss deliberate efforts of providers to meet their obligations to improve the quality of patient care through clinical and managerial changes in the processes of care. Health care practices have always evolved, but mostly in a scattershot way. In recent years, providers have initiated new methods, some of which were modeled first in manufacturing to make ongoing improvements more systematic, data-guided, and efficient (5, 6). These continuous quality improvement methods are commonly referred to as *QI*.

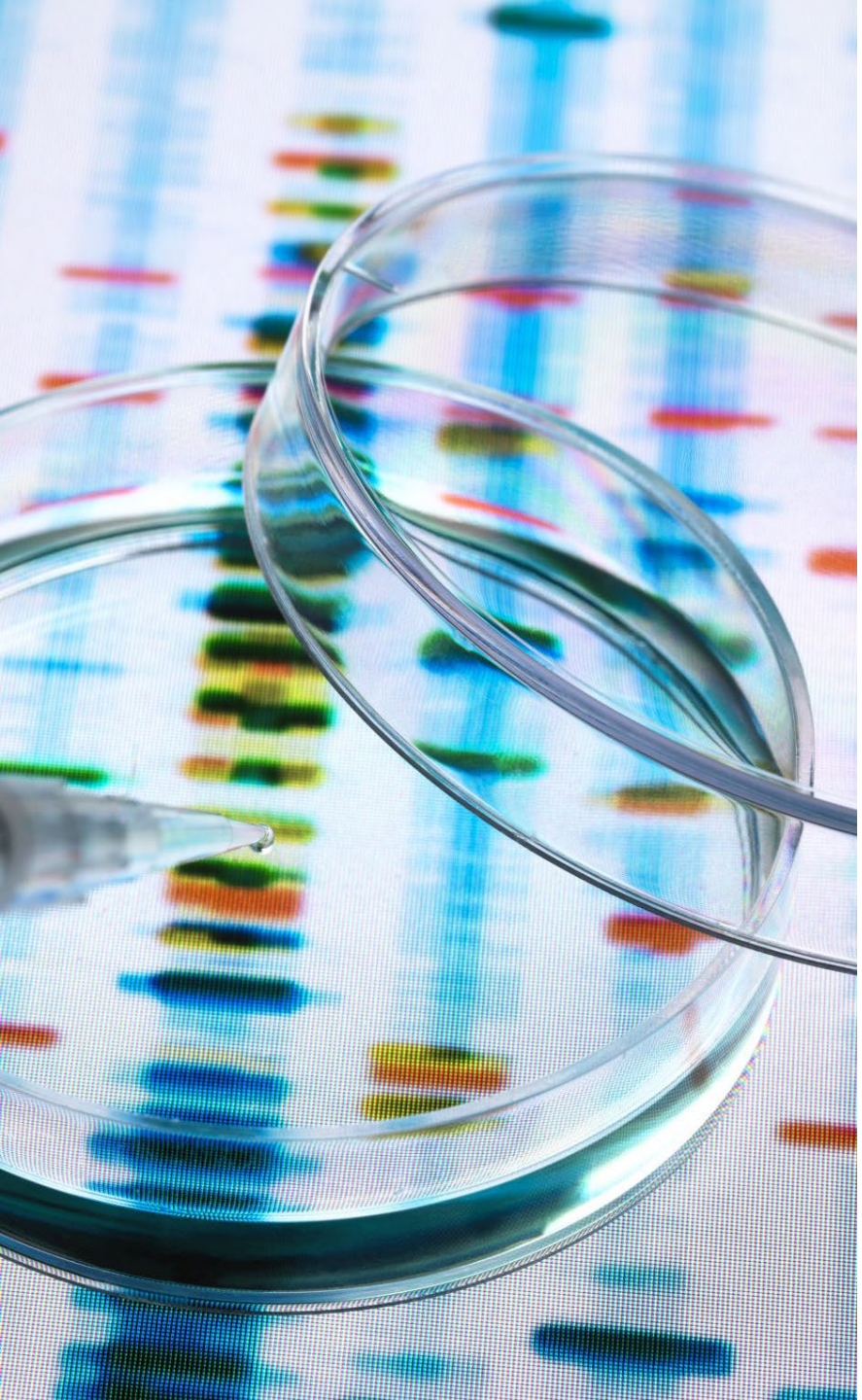
Ethical issues arise in QI because attempts to improve quality may inadvertently cause harm, waste scarce resources, or affect some patients unfairly. For example, efforts at earlier administration of antibiotics for pneumonia may lead to overuse, or efforts to encourage cancer screening may prompt useless, risky, and expensive tests in people who are too near death to benefit. In addition, some activities using QI methods have been categorized as research that uses patients as subjects, which brings the activities under the ethical and regulatory requirements governing human subjects research, including review by institutional review boards (IRBs) (7). Putting improvement activities under research regulations can precipitate substantial delays, costs, and conflicts (8–11). Key federal agencies have disagreed about the boundaries between research and QI, and QI practitioners, health care organizations, agencies that fund research, policymakers, and IRB members are uncertain about ethical and legal requirements. The situation has already generated disincentives to engage in QI.

Beginning in 2003, The Hastings Center convened a group of experts to address the ethical issues associated with QI methods in health care. Ethicists, clinician leaders, experienced managers, regulators, authors of relevant publications, and others met repeatedly, considered published and newly commissioned scholarly papers, and discussed options with experts and affected parties. The project presented interim findings at national meetings on research ethics, general internal medicine, health services research, and quality improvement, and the project sponsored a listserv to share progress and issues with everyone who expressed interest in the work. The project has published a comprehensive report (8) and a set of commissioned papers (12). We present a summary and explanation of the report's main conclusions, along with recommendations for developing policy and practices to protect patients from both the harm that QI activities might cause and the harm that quality and safety deficits do cause. The full report contains more details on the process, the arguments, and our conclusions.

QI Activities: Part of Normal Health Care Operations

The project group addressed 3 questions: What is QI, and what role does it play in health care? What ethical requirements should QI activities meet? What arrangements do we need to ensure the ethical conduct of QI?

See also:
Print
Editorial comment. 680
Web-Only
Conversion of figure and tables into slides



Does the Research Involve Human Subjects?

Common Rule Definition of Human Subject:

any *living* individual about whom an investigator conducting research obtains information or biospecimens:

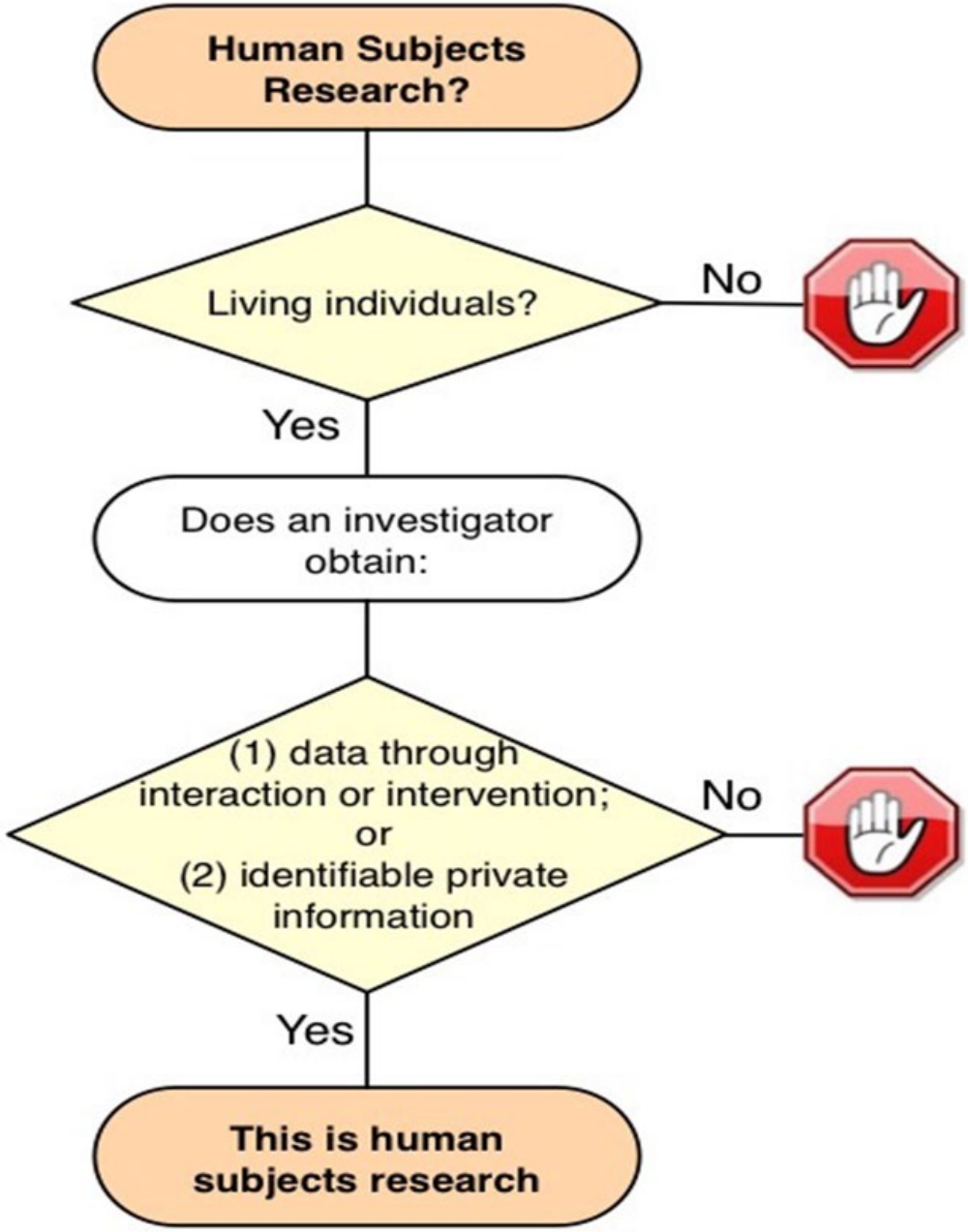
- through intervention or interaction with the individual, and uses, studies or analyzes the information or
- obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

FDA Definition of Human Subjects:

an individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be either a healthy human or a patient.

If for the purpose of a research study…	Then…
An investigator: • interacts with a living individual, • asks them to take part in an intervention, • manipulates their environment, or • collects identifiable materials about them	The research likely involves human subjects.

Does It Involve Human Subjects?



Identifiable Private Information

- The determining factor here is whether the information or biospecimens are identifiable—that is, the identity of the person is either known or can be readily ascertained by the investigator or the research team.
- Researchers may or may not have interacted or intervened with the subject at all – e.g., leftover blood samples from clinical tests; but if the blood sample is identifiable, then the person is a human subject

What about decedent information?

- Although decedent research is not considered human subjects research, the Ochsner IRB requires notification because the IRB doubles as the Privacy Board responsible for HIPAA Compliance.
- To use or disclose PHI of the deceased for research, covered entities must obtain from the researcher who is seeking access to decedents' PHI oral or written representations that
    1. the use and disclosure is sought solely for research
    2. the PHI is necessary for the research, and
    3. documentation, at the request of the covered entity, of the death of the individuals whose PHI is sought

Is the Human Subjects Research Exempt?

- Investigator must submit proposed research study and request for exemption to the IRB
- The IRB Chair, or experienced IRB voting member designated by the Chair, determines whether to grant exemption and records the determination

Is the Human Subjects Research Exempt?

- There are 8 exemption categories listed in the revised Common Rule.
- Most institutions require that investigators submit proposed research to the institution's HRPP or IRB office for the determination about whether it meets the criteria for an exemption.
- Change to the research might make it non-exempt so give us a call and we can advise you .

Category 1: Research in Established or Commonly Accepted Educational Settings

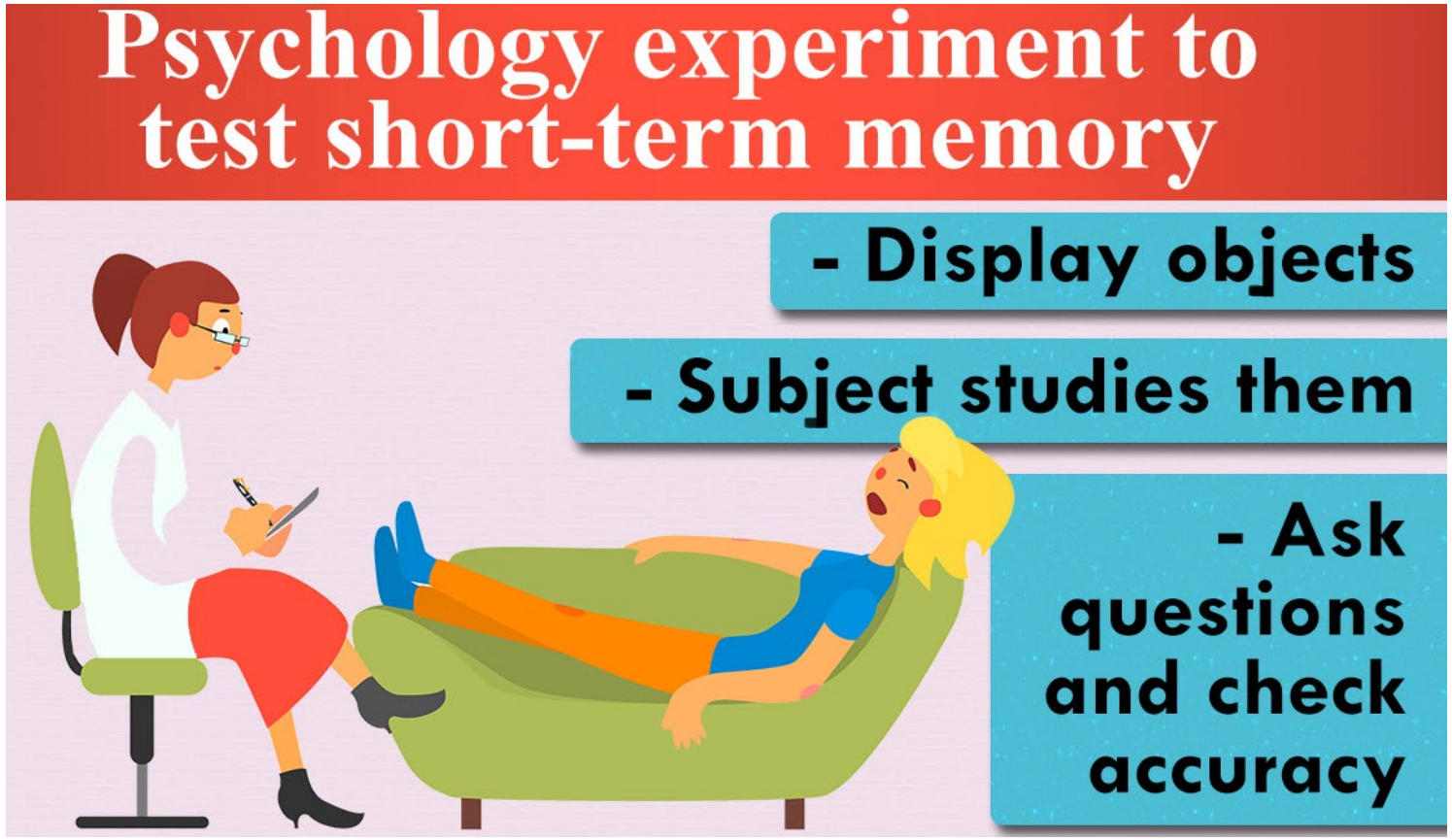
- specifically involves normal educational practices not likely to adversely impact students' opportunity to learn or the assessment of educators who provide instruction.
- includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods
- Example: Comparing instructional practices for CME or professional development

Category 2: Educational Tests, Surveys, interviews, Observations of Public Behavior

Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or audio recording) if at least one of the following criteria is met:

1. Information obtained is not identifiable
2. Disclosure outside of the research would not put subjects at risk of harm (low risk)
3. Information obtained can be identifiable, but the IRB has done a limited IRB review for protecting privacy and maintaining confidentiality

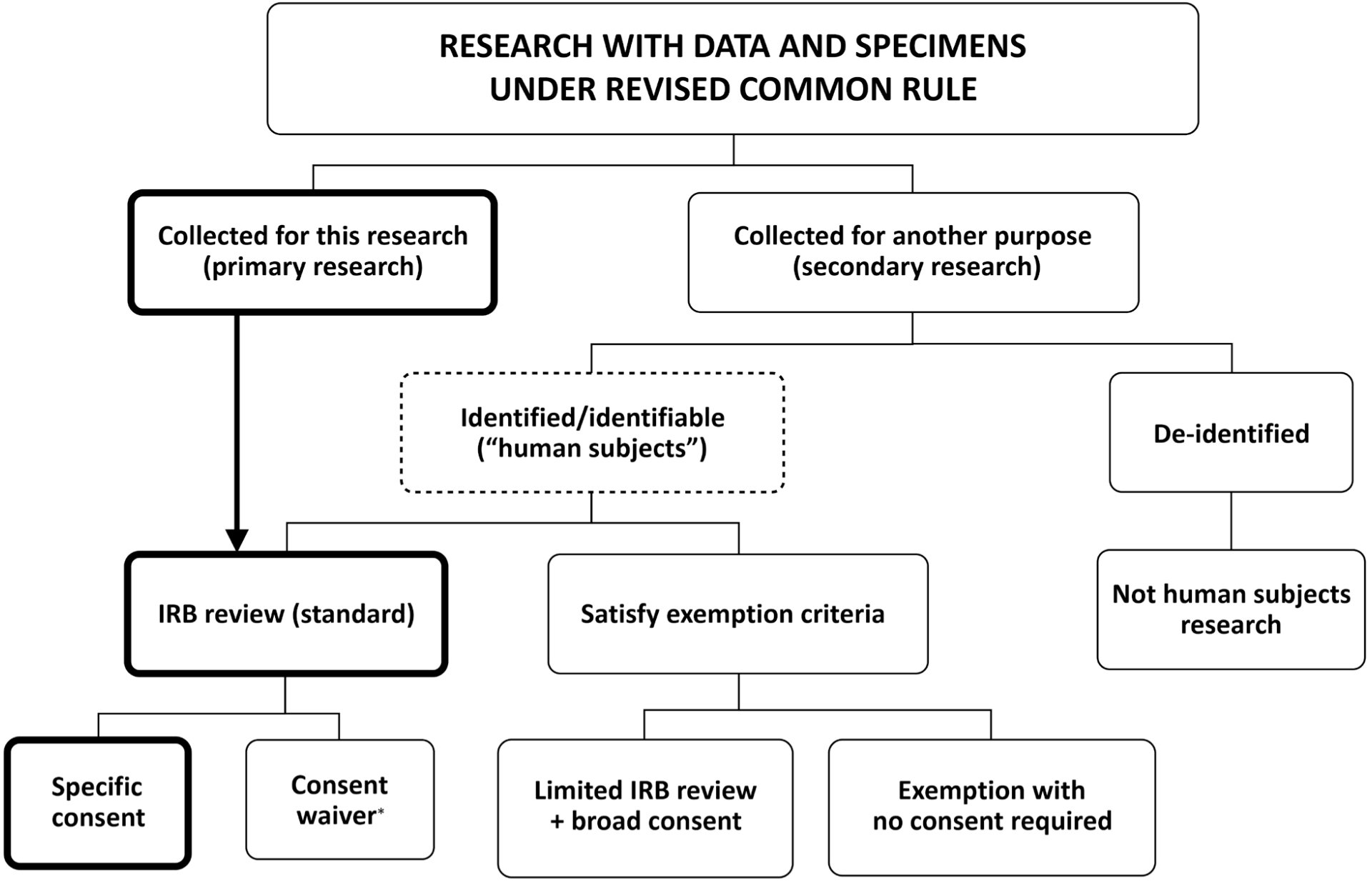
Category 3: Benign Behavioral Interventions in Conjunction with the Collection of Information From Adult Subjects



- Only for research with adults
- Benign behavioral interventions are defined as "*brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing*" (HHS 2017).
- E.g. solving puzzles under various noise conditions.

Category 4: **Secondary Research** for Which Consent is Not Required

Secondary research uses of **identifiable private information** or identifiable **biospecimens**. Data do not need to be existing ("on the shelf") at the time of the research study, can be collected prospectively



**When data or specimens are collected for primary research purposes, consent waiver criteria generally will not be satisfied.*

What is Secondary Research?

Research use of information or biospecimens originally collected for:

- **Non-research purposes** (e.g., leftover blood from routine clinical tests, information entered into Epic for the purposes of clinical care)

OR

- **Research studies other than the proposed one** (e.g., blood samples left over from a study evaluating a new diabetes drug later used for a new study on genetic predisposition of diabetic patients to Alzheimer's disease)

What is *Not* Secondary Research?

It is ***not*** secondary research when investigators interact or intervene with living individuals to obtain their data or biospecimens ***specifically for the proposed research***

Secondary Research with Nonidentifiable Materials

- Secondary research use of **nonidentifiable private information** or **nonidentifiable biospecimens**:
  - Does not involve human subjects, and therefore,
  - *Can either be ruled exempt or certified as Not HSR*

Example:

An investigator downloads data from the National Health and Nutrition Examination Survey and analyzes levels of Vitamin D in the South as compared to other areas of the US

nhanes

National Health and Nutrition Examination Survey

Exemption 4: Secondary Research Use of Identifiable Private Information or Identifiable Biospecimens

I. Identifiable materials are publicly available, OR

II. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot be readily ascertained directly or through identifiers linked to the subjects, and the investigator does not contact the subjects or re-identify subjects, OR

iii. Investigator's use is regulated under HIPAA as *"health care operations," "research,"* or *"public health,"* OR

iv. Research is conducted by, or on behalf of, a Federal agency using data collected or generated by the government for non-research purposes, and the information is protected by federal privacy standards

Category 5: Research and Demonstration Projects that Are Conducted or Supported by a Federal Department or Agency

Category 6: Taste and Food Quality Evaluation and Consumer Acceptance Studies

Category 7: Storage or Maintenance for Secondary Use for Which Broad Consent is Required

Category 8: Secondary Research for Which Broad Consent is Required

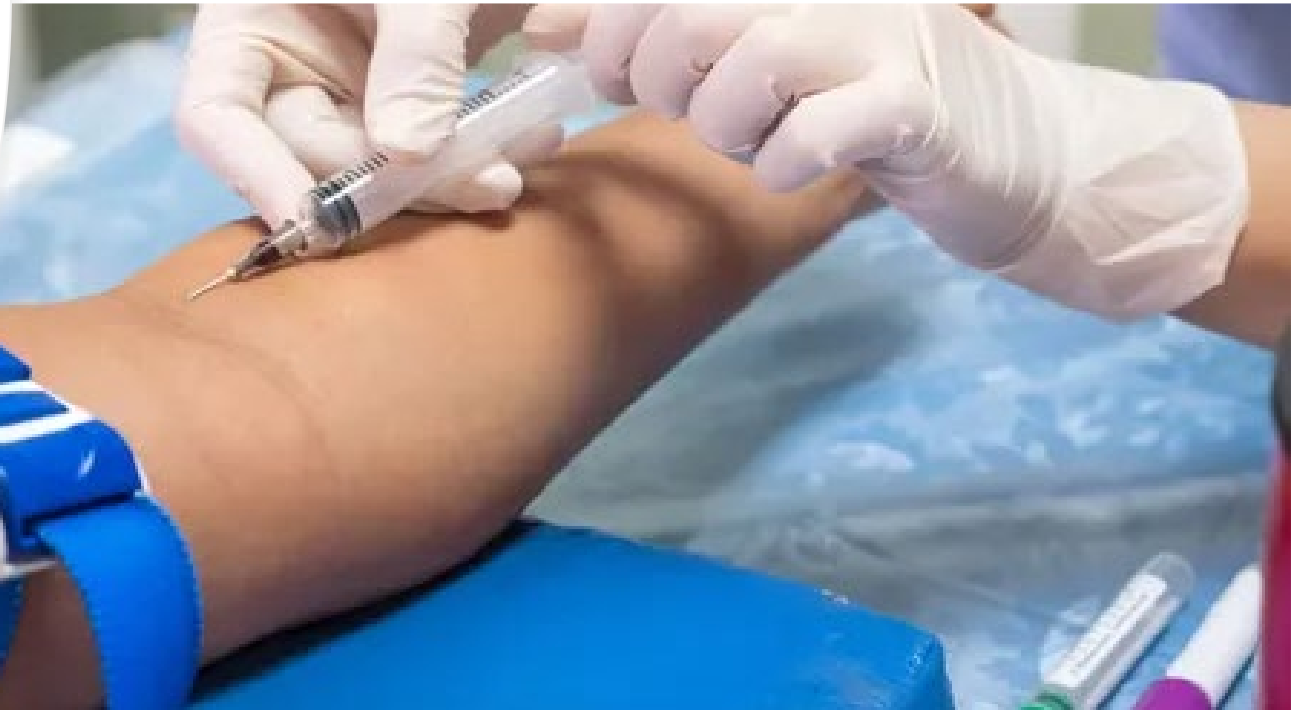
Why don't we use broad consent?

- Obtaining broad consent in a clinical setting is challenging
- If a person refuses, their biospecimen must be tracked to make sure it is not later used in secondary research that could fall under that broad consent
- Tagging and tracking consent (and refusal) is expensive given the low-risk nature of biospecimen research
- Institutions may not have resources required for tracking broad consent within institutions

Lynch, H., Wolf, L., & Barnes, M. (2019). Implementing Regulatory Broad Consent Under the Revised Common Rule: Clarifying Key Points and the Need for Evidence. Journal of Law, Medicine & Ethics, 47(2), 213-231. doi:10.1177/1073110519857277

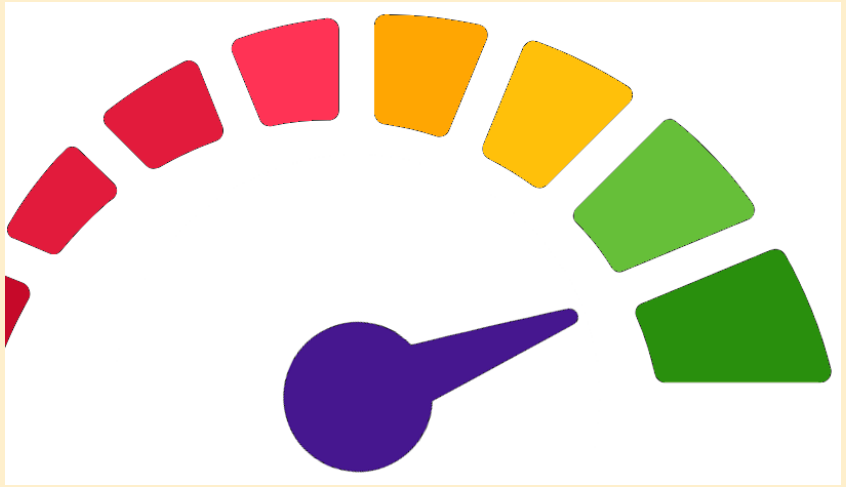
Is It Minimal Risk?

"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 of the general population or during the performance of ***routine*** physical or psychological examinations or tests."



Is It Minimal Risk?

- While the harms and discomforts ordinarily encountered differ widely among individuals and individual populations, an ethically meaningful notion of MR should reflect "background risks" that are familiar and part of the routine experience of life for "*the average person*" in the "*general population*."
- It should NOT be based on those ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population e.g. patients undergoing chemotherapy for cancer, individuals with ESRD on HD.



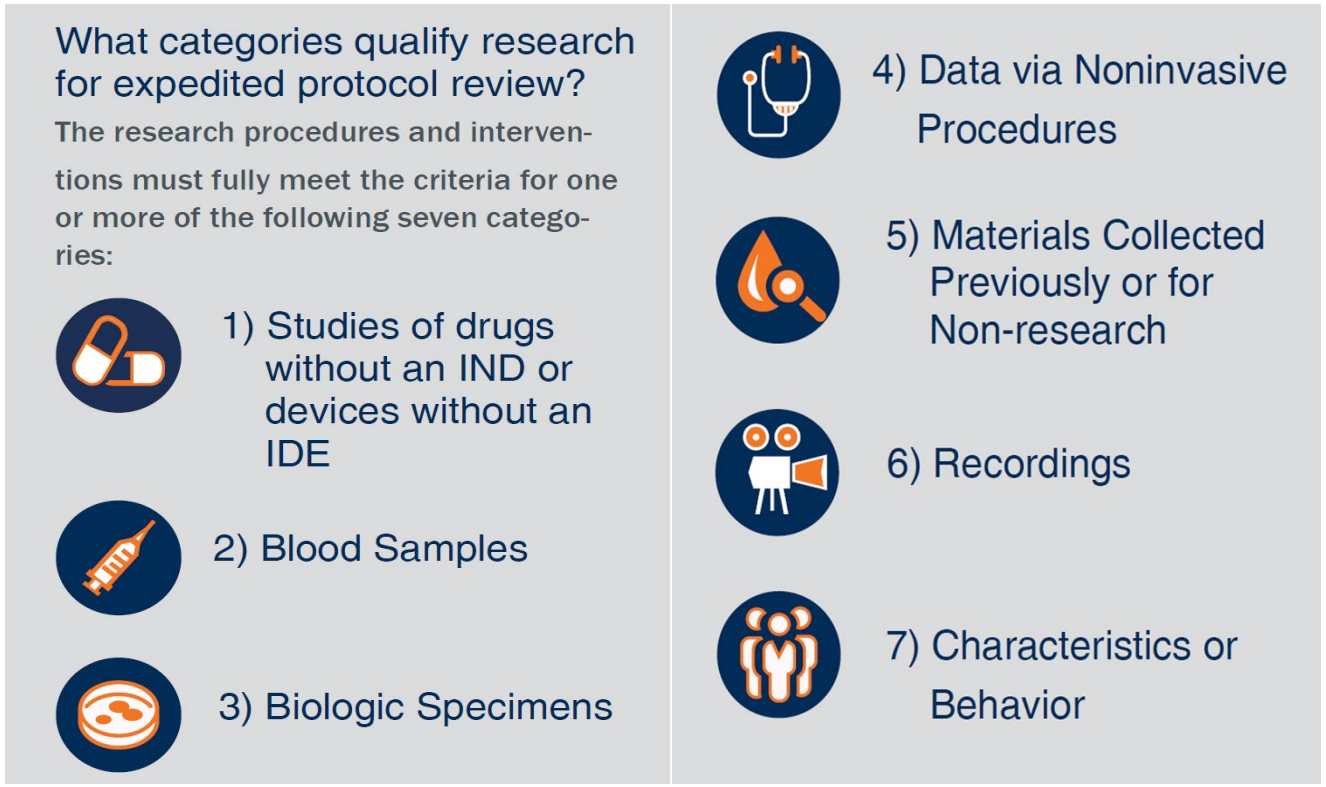
What is Expedited Review?

- A type of review whereby the IRB Chair or one or more experienced IRB members review in lieu of the full board.
- Allow some minimal risk research and minor changes to approved research to be reviewed without waiting for a meeting of the convened IRB.
- May approve or require modifications. If the reviewer cannot approve, the research goes to full board.

Expedited Review

For research to be reviewed using the expedited review procedure, it must:

- Present no more than minimal risk to subjects.
- Involve only procedures listed in one or more of the expedited categories.



1) Studies of drugs without an IND or devices without an IDE

Clinical studies of drugs and medical devices ony when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2) Blood Samples

Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) **from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, 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**

(b) **from other adults and children[2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, 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) Biologic Specimens

Prospective collection of biological speciemens for research purposes by noninvasive means

(a) hair and nail clippings in a nondisfiguring manner;

(b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

(c) permanent teeth if routine patient care indicates a need for extraction;

(d) excreta and external secretions (including sweat);

(e) 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;

(f) placenta removed at delivery;

(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

(h) 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;

(i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

(j) sputum collected after saline mist nebulization.

4) Data via Noninvasive Procedures

Collection of data through noninvasive procedures* routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

(a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

(b) weighing or testing sensory acuity;

(c) magnetic resonance imaging;

(d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

(e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

*Not involving general anesthesia or sedation.

5) Materials Collected Previously *or for* Non-research Purposes

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) Recordings

Collection of data from voice, video, digital, or image recordings made for research purposes.

7) Characteristics or Behavior

Research on individual or group characteristics or behavior, including (but not limited to)…

- Perception
- Cognition
- Motivation
- Identity
- Language
- Communication
- Cultural bliefs or practices, and social behavior

Research employing the following methodologies:

- Survey
- Interview
- Oral history
- Focus group
- Program evaluation
- Human factors evaluation
- Quality assurance

Convened (Full Board) Review

- Greater than minimal risk
- Minimal risk research that does not qualify for expedited review

Convened (Full Board) Review

- A majority of members must be present, including a non-scientific member
- In order for the research to be approved, majority must vote to approve

Criteria for Approval

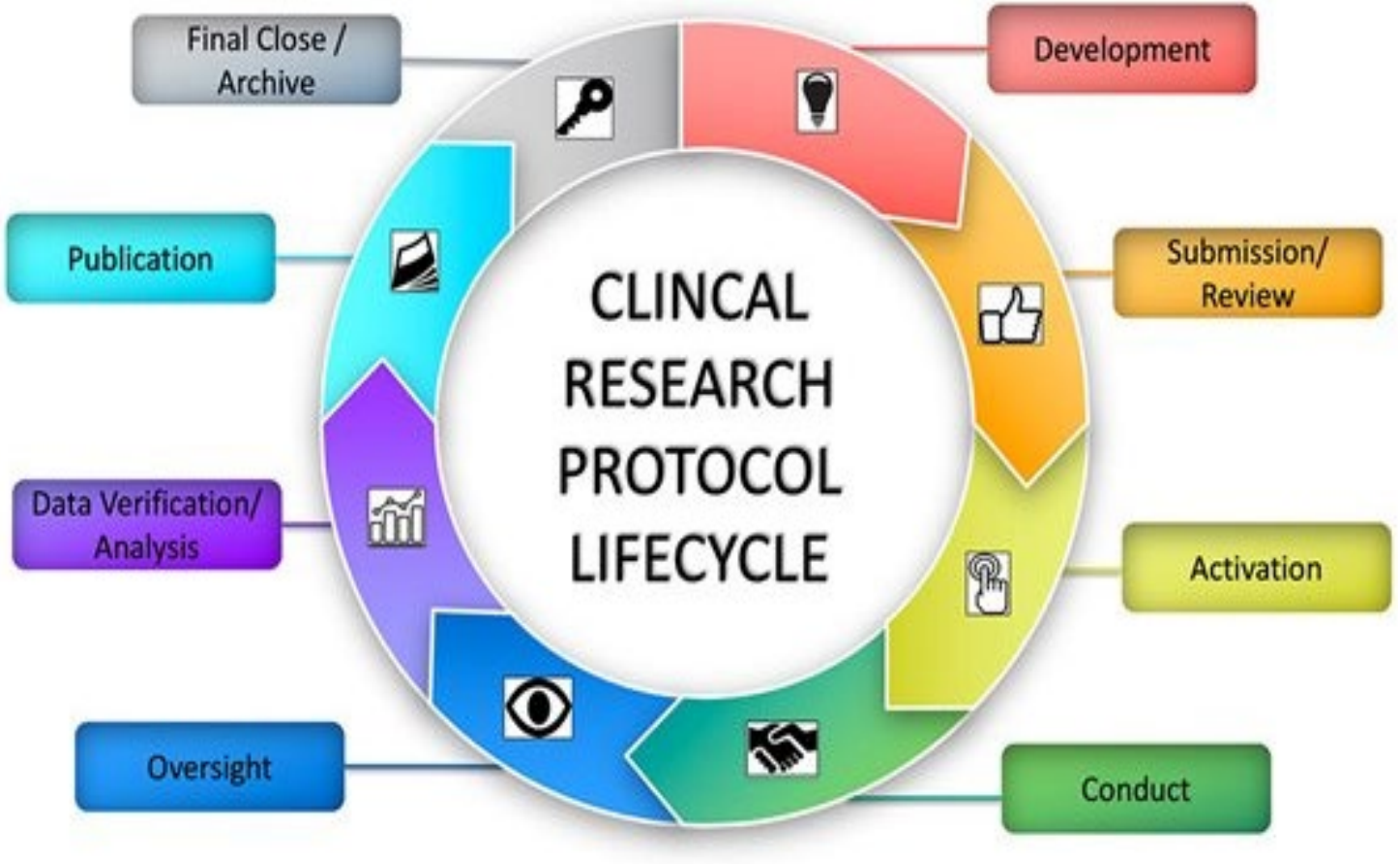
- that risks to subjects are minimized through sound research design and are reasonable in relation to anticipated benefits and knowledge gained;
- that the selection of subjects is equitable such that no population or subpopulation bear an imbalance of the burden of research or enjoy an inequitable share of the benefits;
- that the informed consent process and documentation plan is appropriate;
- that the safety of the study is protected by an appropriate plan and monitored by an independent party, if needed;
- that the privacy of subjects and the confidentiality of study data is protected; and
- that adequate protections are in place for vulnerable populations.

The IRB may act on an application in one of four ways:

- The application may be approved;
- The application may be approved with administrative changes that must be completed by the PI;
- The application may be tabled pending submission of revisions; or
- The application may be disapproved.

Lifecycle of IRB Submissions

- Initial Submission
- Continuing Review
  - Typically, annual
- Modifications
  - Anytime there are changes to the protocol or documents associated with the study
- Reports of New Information
  - DSMB Reports
  - Protocol deviations
- Study Closure once all follow-up is completed



Questions

- We know this can be challenging
- We are available for questions about your research and its review. Call us, we can help you! x23535 or irb@ochsner.org