

Session 4: Human Subject Protections & Regulatory

Tip: This handout refers to several regulations which may be important for you to review. Rather than include them all within the document, some of them being lengthy, I have cited the relevant regulations. Here is a very helpful, well-organized site to find the regulations quickly: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>. If this URL does not work for some reason, you can usually Google the specific regulation (e.g., “45 CFR 46.111”) and find it fairly easily.

I. Fundamental Ethical Principles and Research Regulations

History has seen humans tortured, killed, misled, and exploited for the sake of social and behavioral research. In response to egregious research activities, a series of codes of human research conduct were developed over the 20th century. It wasn't until 1981 in the United States that research regulations were codified on the heels of a scathing expose published by Henry Beecher and the outing of the infamous Tuskegee study. The US regulations were based on the landmark work of the Belmont Commission which was tasked with identifying core ethical principles that should guide human research. The Belmont Report discussed three core principles that all research should follow:

- 1) **Respect for Persons**; that participation in research should be voluntary and that all individuals' autonomy in deciding whether or not to participate in research must be respected.
- 2) **Beneficence**; that researchers should show kindness that goes beyond mere obligation in seeking the welfare of research subjects.
- 3) **Justice**; that subjects are selected fairly and that the populations undergoing risk in research should be the same populations that will ultimately benefit from the work.

The Common Rule regulations (45 CFR 46) describe the function of Institutional Review Boards (IRBs) that must review and approve federally-funded research. The regulations describe the conditions that must be met for an IRB to approve a research project (45 CFR 46.111), which derive directly from these three ethical principles:

- 1) The risks to subjects have been minimized [*Beneficence*]
- 2) The risks to subjects are reasonable in relation to anticipated benefits of the research [*Beneficence*]
- 3) Selection of subjects is equitable [*Justice*]
- 4) Informed consent will be sought from each subject [*Respect for Persons*]
- 5) Informed consent will be appropriately documented for each subject [*Respect for Persons*]
- 6) When appropriate, the study is adequately monitored during its conduct to ensure subject safety [*Beneficence*]
- 7) Subject privacy and confidentiality is adequately protected [*Beneficence*]
- 8) When enrolling individuals who are vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons), additional safeguards have been included to protect their rights and welfare [*Respect for Persons, Justice, Beneficence*]

It is important for researchers to be aware of these regulations for a couple main reasons. First, the regulations provide a structured guide to thinking about the ethics of your study. However, the regulations should be considered a minimum requirement for ethical research design; investigators and IRBs can go beyond what is strictly required by

the regulations when it helps protect subjects to the fullest. Second, knowing what IRBs must consider helps you communicate to IRBs through your protocol and submission documents

In designing your research, you need to make sure these points are covered, incorporated into your study design, and then communicated to the IRB. For the purposes of this workshop, you will write a paragraph detailing the main human subject protection concepts. **At UCD, COMIRB has a thorough protocol Application which asks for details to support all of these points; therefore, this information will go in your Application and not actually end up in your protocol if submitting to COMIRB.** Knowing the big picture of how you have considered and addressed these points will help you appropriately complete the Application form. Let's review considerations for the eight criteria...

A. Criteria #1 and #2 (Risks to subjects are minimized and are reasonable in relation to anticipated benefits of the research)

Addressing these two criteria requires you to analyze both the risks (#1) and the benefits (#2) of your research. When doing so, it is important to note the wording of #2; you are balancing the risks to individual subjects against the benefits of the research as a whole. There does not need to be direct benefit to individual subjects; however, there must, at minimum, be the benefit of generalizable knowledge that will come from the research. For this reason, the IRB has every right to question your study design – the design of your study must allow for conclusions that will advance science (e.g., adequate controls, confounders minimized, subjectivity/variability minimized), or the benefits of the research can never outweigh the risks to individual subjects.

- i. Risk Analysis: Every research study has potential risks; at minimum, there is a risk of loss of confidentiality of subjects' data. Loss of confidentiality may be the only risk of your study, but it is important to acknowledge this risk (it's OK to acknowledge it as "minimal risk"). After confidentiality, you must consider any other risks of your research that derive from your study procedures; most study procedures will have an associated risk.

Correctly identifying all of your study procedures is actually more difficult than it sounds, especially when your research intertwines with medical care. It is easy to under- or over-identify study procedures. The best way to identify study procedures is to consider the following formula:

[Subject experiences in the study] – [Subject experiences if not in the study] = Study Procedures

If something would have happened to a subject anyway if there were no study, then that occurrence is not a study procedure. If it happens because they are in the study, then it is a study procedure. Here are a couple examples:

Example 1: For treatment of a hip condition, it is standard care to obtain X-rays every 6 months for 2 years. If the protocol states that "We will assess treatment effect by assessing X-rays performed every 6 months for 2 years," this statement indicates that the protocol mandates these X-rays be done and the X-rays are a study procedure. What is likely more accurate is to state "Results from standard of care X-rays done every 6 months will be used to assess treatment effect." This second version makes it clear that the study is not dictating the performance of X-rays and therefore the X-

rays are not study procedures. It also means that if the provider determines that an X-ray is not clinically warranted for whatever reason, it would not be performed and the result would be unavailable for use as study data.

Example 2 (more subtle): “All subjects must be treated with either levofloxacin or ciprofloxacin for their UTI” vs. “All subjects will have been prescribed either levofloxacin or ciprofloxacin for their UTI”

The first statement indicates that once a subject is enrolled, s/he must be given one of two antibiotics for his/her UTI; the protocol dictates the choice of care and narrows it from many choices a provider may use, down to two. It may well be that each subject would have received one of these drugs anyway, but there would have been a provider-patient decision of which to use; this decision has been taken away within the study and the protocol now dictates care. The provision of antibiotic for the UTI becomes a study procedure, and the risk of each antibiotic is a study risk. The second statement indicates that subjects are only in the study if the patient-provider unit has decided on one of these two treatments (i.e., an inclusion criterion). The study has not affected this treatment decision, and the treatment of UTI is not a study procedure or a study risk.

Assess every study procedure for possible risk. Questionnaires/interviews can have risks other than just confidentiality – consider a questionnaire about past traumatic experiences which could trigger anxiety or PTSD symptoms; even a questionnaire about deeply personal attitudes or practices can cause embarrassment or shame and should be acknowledged as a risk. Mild physical or emotional discomfort can and should be listed as a risk. Obviously, more significant pain, injury, or adverse reaction that can result from study procedures should be listed. Any form of radiation, even though it typically does not cause discomfort, is a risk.

If your study includes an intervention, consider both the intervention and the control arms for possible risk. Sometimes the control arm can actually have different risks than the intervention arm.

In general, you need to think like an IRB does in assessing risk, being skeptical of the study's safety. If the IRB can think of risks that you do not describe and address, you have a lower likelihood of having your study approved without further work. Highlighting potential risks will not harm to your study; only failing to minimize those risks will harm it.

You must then also think to yourself whether you have adequately minimized the risks. Have the procedures that carry risk been kept to the minimum number needed to answer your question (can you answer the question just as well with 3 X-rays as opposed to 4)? Could you substitute less risk procedures for the ones you have proposed? Are there any procedures that are not necessary to answer your question? Are there procedures that do not clearly inform one of your outcomes (if so, it either needs to be eliminated or you have forgotten an important outcome/specific aim)? You should be the one to propose how you will minimize risks. You may not like a proposed solution that an IRB requires to mitigate a potential risk, but this is the reality of a system of third-party review. The best strategy is to *proactively* identify and anticipate potential risks, and then frame arguments to the IRB why those risks have already been minimized and are acceptable in light of the study's benefits.

- ii. Benefit Analysis: Every study must have some *potential* benefit, or it would be unethical to allow it to occur. The nature of research (and one of its official regulatory definitions, in fact) involves its intention to produce *generalizable knowledge* (new knowledge about universal truths). If all your study offers is individual subject benefit, then it is really just treatment/intervention and not research. Your benefit statement should include an argument of why the knowledge gained will benefit society. **The core decision of weighing benefit against risk lies in the importance of the knowledge to be gained.** This hopefully illustrates why a well-communicated background section and sound scientific design are so crucial to an IRB; if your theory is good, but your methods are flawed and cannot result in generalizable knowledge, the research cannot be approved.

In addition to generalizable knowledge, think of how else there might be *potential* benefits to individual subjects (just a bonus on top of generalizable knowledge). Subject benefit typically falls into one of the following categories:

- a. Potential therapeutic benefit: that one or more study arms *might* receive a therapeutic benefit from being in the study
- b. Potential diagnostic benefit: Perhaps you are doing some procedures that identify a medical condition earlier than it otherwise would be caught. You can only make this claim if the findings are actionable (i.e., if your hypothesis is that a test will detect a condition and you are comparing to a gold standard done later, you cannot claim the individual experienced a benefit)
- c. Potential educational benefit: Perhaps the subjects, by virtue of participating in the study, will learn about themselves or their medical condition that could have meaningful impact on their personal futures.

B. Criterion #3 (Selection of subjects is equitable)

A question sometimes received by the IRB is “Aren’t you supposed to be protecting subjects? Then why do you need to review my study advertisement?” Well, this is why. The IRB is to ensure subjects are selected equitably. Identifying subjects is the first step in selecting them, and selecting them is the first step in enrolling them. Because of the importance of selection in ultimate enrollment, regulatory authorities have included the review of recruitment methods to be part of this assessment. But consider the following important points as well. Subject identification and recruitment touches on criterion #7 and the HIPAA rule (individual privacy). Subject recruitment also relates to criterion #8 (vulnerability); how a study is pitched to a desperate population will shape what they think/hear during the consent process. Finally, the way you select your study sample can directly impact the quality of your study results (if subjects are selected with bias, that bias will carry over to your results). Recruitment methods are more complex and important than they seem on the surface, which is why they are scrutinized by IRBs.

In general, here are key points about how subjects are identified and recruited:

- i. Objective and unbiased methods of identifying and selecting subjects: Random selection from a population promotes obtaining a representative sample. Subject selection for research is rarely random and instead typically takes the form of convenience sampling (sampling what is nearby or convenient). If not random, are you approaching everyone in your local environment? If not approaching everyone, how can you increase the rigor or randomness of how you are approaching potential subjects so that

unconscious biases are not affecting your selection? Recruiting from your medical practice is a common technique. If it is not possible to approach all potentially eligible subjects, incorporating some random selection elements into your selection might be beneficial (e.g., from a list of possible subjects to approach, you will flag every n^{th} person to approach).

If you are using advertisements, where are you posting them? Who is likely to see them? Who is likely to respond to them? Is the wording used objective, or is it likely to catch the attention of a certain subgroup of the population? Are you overemphasizing compensation, provision of medical services, or a societal benefit of participating in your research?

- ii. Exploitation or Improper exclusion: The ethical principle underlying equitable selection dictates that the same people undergoing risk in research should be of the same population that will someday benefit from the research findings. Is this true for your study? If there are individuals being recruited for a study to develop a drug, but these individuals come solely from a group that has little hope of ever accessing this drug, that is unjust. If subjects are being recruited because they are an “easy target,” “a captive audience,” “ever willing,” or “in need of care,” this might be exploitative. If specific individuals are not being considered (e.g., women, non-English-speaking) without a scientific justification for their exclusion, this is improper exclusion. When communicating your recruitment methods to the IRB, it should be clear that elements of exploitation or improper exclusion are not present. If there is a gray area, proactively highlight this area and explain how you will minimize the issue.
- iii. Invasion of privacy: You need to be sensitive to invading someone’s privacy when recruiting for research. With access to medical records, you may actually know quite a bit about potential subjects before you approach them to be in a study. If you have never personally seen a patient clinically, and then call them out of the blue and tell them that you know about their recent surgery and that their last CD4 count was less than 100, they are likely to feel violated, angry, and confused. However, if you start by explaining that you work in the hospital HIV clinic that they have attended, with their provider, and you are conducting research on recent surgical procedures in patients with HIV, the individual might be more receptive. A good rule of thumb is to ask yourself, “Would the patient be surprised that I am contacting them?” If the answer is yes, you need to think of how to prevent this surprise.

A “yes” answer to that question also means your recruitment plan likely violates the HIPAA rule (more on this in the HIPAA section later in this document). HIPAA is intended to prevent improper access and use of individual’s health information. If you or your Department is not somehow involved in the care of a group of patients, you may have limited options in accessing the group’s medical information for research purposes.

C. Criteria #4 and #5 (Informed consent will be sought from, and documented for, each subject)

The principle of Respect for Persons dictates that individuals voluntarily choose to participate in research. In order to make a true decision, they must have sufficient information about participation so that they can make an informed judgement of whether or not they should participate. The Regulations describe the minimum necessary elements to be communicated to a potential subject to obtain truly informed consent in 45 CFR 46.116 [a] and [b].

- i. Obtaining informed consent. A common misconception is that informed consent is the form that a person signs to agree to participate. In contrast, the form is merely the documentation of their consent. True informed consent is a process of information exchange between investigator and potential subject. It is an ongoing process that continues until the potential subject has received sufficient information to make an informed decision.

You will need to describe your plan (consent process) for how and when you will obtain consent. The IRB will need to be able to visualize that process and know that it is unhurried and unpressured, and that correct and sufficient information will be provided. The consent form (the consent form becomes very important to the IRB in terms of judging whether adequate information will be provided during the consent process). Overall, make sure that you are communicating that you understand consent is a process.

There are certain types of studies where informed consent cannot really be obtained (e.g., retrospective chart reviews and studies requiring deception - behavioral studies where giving full details of the purpose of the study would bias subject behavior and therefore outcomes). The regulations do have provisions for a **waiver of informed consent**, where informed consent is not required. The provisions are described in 45 CFR 46.116[d]; key provisions are that the research poses only minimal risk to subjects and that it is impracticable (= not possible) to conduct the research if informed consent were required. “Impracticable” is different than “impractical;” the IRB will not accept an argument that it is too hard or inconvenient to obtain consent – it must truly not be possible to conduct the research. Note that it is not possible to waive consent if your research poses greater than minimal risk (see risk determination in section IV.D).

A common mistake is to state that it is impracticable to obtain informed consent because you are not going to be face to face with potential subjects (e.g., internet or mail survey research). It is possible to deliver the elements of informed consent via writing, and accompany that with a phone number to call for any questions; such a method is sufficient in simple low-risk studies to obtain informed consent (if not face to face with subjects, you may not be able to *document* informed consent, but this is separate from obtaining informed consent).

- ii. Documentation of informed consent. Informed consent must also be documented by having the subject sign a consent form. The consent form must document the required elements laid out in 45 CFR 46.116 [a] and [b]; the COMIRB consent template is designed to have all of these elements. It is generally advisable to use the COMIRB consent template; however, simple questionnaire or prospective observation studies, may consider using the COMIRB postcard consent template (one long paragraph). It is also possible to waive documentation of consent (see 45 CFR 46.117 [c]). This is usually done in internet or mail survey research when you are not face-to-face with potential subjects. Note that waiver of documentation of informed consent usually applies to minimal risk research.

D. Criterion #6 (When appropriate, the study is adequately monitored during its conduct to ensure safety)

Your protocol and IRB application describe the anticipated risks of your study, and the IRB approves your research based on these anticipated risks. But once you start the study, how will you ensure that you had adequately anticipated the risks?

Simply put, you must have some sort of plan to monitor the safety of your study as it is in progress to ensure there is not an unanticipated risk signal. The plan should always begin with your intention as the PI to monitor for unanticipated problems (unexpected harms to subjects that arise because of the research); this is usually sufficient for minimal risk studies.

From there, the plan should be appropriate for the amount of risk in your study. In a stepwise ascending order, you might propose periodic review of adverse events; you might have a medical safety officer providing oversight of adverse events; you might have an internal data monitoring committee (a committee of experts that is not independent of the research team) watching the safety signal; or, you might need a Data Safety Monitoring Board (a committee of medical and statistical experts that is *independent* of the research team...this is usually reserved for large, multisite trials).

Use common sense in deciding on a plan for safety monitoring. What would make you comfortable that you will identify any safety issue that you did not anticipate? And remember...all studies have potential unanticipated problems – at minimum, potential breach of confidentiality is an event you need to monitor for and report to the IRB if detected.

E. Criterion #7 (Subject privacy and confidentiality is adequately protected)

Privacy refers to an individual limiting others' access to their personal information. Protecting a subject's privacy involves not putting subjects in positions where they cannot control access to their information. For example, if you are conducting an interview, that you conduct it in a location that is sufficiently private and the subject's answers will not be overheard.

Confidentiality refers to a person protecting others' private information. As an investigator, it is your obligation to safeguard the data you collect and prevent it from becoming known to anyone outside of the research team. Your research data should not be stored on flash drives, laptops, or desktops which can be easily stolen. It is preferred to store data on secure, partitioned Division servers that have access restricted by user. The CCTSI also offers a secure, professional research database system known as REDCap that is web-accessible; this is a great option to look into for secure storage. Overall, make sure you have a secure location with limited access by others. Any paper documents (including signed consent forms) must be secured under lock and key inside a locking office.

F. Criterion #8 (Protection of vulnerable subjects)

Vulnerability in research refers to the inability to make a free, informed decision about joining a study. The inability to make a free, voluntary decision could be because of developmental state (fetus, child), or from a tendency to overlook short-term research risks. Subjects might overlook short-term risks of research because they are afraid of a bad thing happening (such as their provider not wanting to provide them with best treatment, or parental disapproval, if they don't join their research), which is *coercion*. Subjects might

overlook short-term risks of research because they want to gain something (such as access to an experimental treatment or a large cash payment), which is *undue influence*.

The “classic” categories of vulnerable subjects identified by the Regulations include:

- Pregnant Women/Fetuses (45 CFR 46.204)
- Neonates (45 CFR 46.205)
- Children (45 CFR 46.404-407)
- Prisoners (45 CFR 46.305-306)
- Mentally Disabled/Cognitively Impaired
- Educationally disadvantaged

There are specific regulations that govern the inclusion of any of these population sin research, indicated in parentheses above. If you are planning to include any of these populations, look up the associated regulations so you can see what is expected in the protection of these subjects; cognitively impaired and economically disadvantaged populations do not have prescriptive regulations. In general, you should think carefully about your subjects and decide if there are any elements of vulnerability that could be present. Vulnerability is often about situations (power relationship, such as provider-patient, professor-student, employer-employee) rather than a pre-defined category. It is up to you, then, to identify any “other” vulnerability and propose methods to minimize the factors creating the vulnerability.

You must acknowledge the inclusion of such populations, **even if you are doing a retrospective chart review**. If you do not plan on including pregnant women or prisoners, you should list them in your exclusion criteria to make it absolutely clear they will not be included.

The following are some important notes about some of these populations:

- i. Children. If you will be enrolling children (<18y.o.), there are special considerations with regard to risk (see section IV.D for risk determination). The review of research that includes children depends on the risk posed to children. If the risk of the research is minimal (46.404), no further considerations are needed. If the risk is greater than minimal, but there is a prospect of benefit of the research to the subjects (46.405), there are no further considerations. It is important to think about each arm of your study separately in this regard; there might be a prospect of benefit only in your experimental group (not in your control group), and these need to be considered separately. If there is greater than minimal risk in any research arm with no prospect of benefit (46.406), there are several additional restrictions on what can be done. And if your research does not fit into any of these categories (46.407), the research an only be performed with an act of Congress (literally).
- ii. Prisoners. Prisoners can be individuals confined in a penal institution, individuals legally confined in other institutions as an alternative to criminal proceedings (e.g., court-mandated substance abuse program, home arrest), or individuals detained pending arraignment/trial/sentencing. If you plan to enroll anyone meeting this broad definition, you need to read through the associated regulations to understand the multiple factors that can influence this population. Your research will need to be reviewed by a convened committee, regardless of the level of risk, under special review procedures.

- iii. Cognitively impaired/decisionally challenged. Common sense tells you that this population needs extra protections. The regulations equate a subject with their “legally authorized representative” (LAR) in terms of consenting to research. Therefore, if a subject’s LAR is available to provide consent, this person can freely substitute for the subject in providing consent. However, there is no law in Colorado that specifies who can legally provide consent to join research for another person. Therefore, the only true LAR in Colorado is someone who has been court-appointed to make all major decisions for the other person. Very few people have true LARs for research in Colorado, and this makes research in emergency care and ICU settings more difficult.

While there is no law regarding consent for research, Colorado law does specify who (referred to as a proxy) can make a medical decision on another person’s behalf when there is no LAR available. The University of Colorado has decided to use this law in order to determine who, other than a true LAR, can provide consent for research; but because it is a medical decision-making law, consenting to the research must be equivalent to making a medical decision. This means that there must be some *potential* medical benefit to being in the research to allow non-LAR proxy consent. This interpretation of law makes observational research in emergency and acute care settings very difficult to conduct. If you are planning research with decisionally challenged subjects that has no potential direct benefit to the subjects, you should talk with COMIRB early on about your options.

II. FDA-regulated Research

Most federal agencies abide by 45 CFR 46, a.k.a. the “Common Rule” (hence the name), but the FDA is not one of them. Their regulations of most relevance to human subject regulations are found in 21 CFR 50, 56, 312. In general, FDA regulations are obtuse and hard to navigate. FDA regulations for the most part mirror the Common Rule regulations, except for a couple important differences (noted below). Because of these key differences, it is important that you identify whether your research is subject to these more restrictive regulations. COMIRB’s forms guide you through the types of information you need to provide for the IRB to evaluate your study with regard to FDA regulations.

A. *When is a study subject to FDA regulations?*

A study must comply with FDA regulations when either: 1) an individual is given a drug as a study procedure (even drugs that are FDA-approved) or 2) the study is evaluating the effectiveness or safety of a medical device. Device studies can be tricky. Medical devices are defined broadly and include software programs and in vitro reagents; basically, almost anything (other than a drug) that is being used to diagnose, treat, prevent, cure, or mitigate a disease or condition. If your protocol is dictating how/when a drug is given to subjects, or is answering questions about how a device works to diagnose or treat a disease, you need to think about FDA regulations.

B. *Differences between FDA regulation and the Common Rule.*

There are three main differences when a study is conducted under FDA regulations, each with important implications (presented briefly):

- i. Definition of research. The Common Rule definition requires the project to be intended to develop or contribute generalizable knowledge. This makes intuitive sense to us when thinking about what research is. However, the FDA definition only requires that a patient is receiving a drug (except for an approved, marketed drug within the course of medical practice) or the project is collecting safety/effectiveness data about a medical device. Generalizable knowledge is not a requirement for the FDA. **Implication:** You might be doing FDA research but not realizing it because you are thinking only in terms of generalizable knowledge.
- ii. Definition of human subjects. The Common Rule requires that data are collected about living individuals through either an interaction/intervention with individuals or through the collection of their private and identifiable information. This definition therefore has a lot of “outs” to keep a project from being subject to the Common Rule (e.g., if all subjects are deceased, the project is not regulated). The FDA only required that a person receive a drug or a medical device is tested on an individual *or that individual’s samples*. There is no requirement for samples to be identifiable or subjects to be living. **Implication:** You might be doing FDA research but not realizing it because you are thinking only in terms of the Common Rule definition of human subjects.
- iii. Allowances for alteration/waiver of informed consent. As discussed above (see section I.C.), the Common Rule allows for waiver of informed consent if certain criteria are met. FDA regulations do not have this same allowance; waiver of consent is only allowed for FDA research in emergency settings with a long list of criteria and responsibilities for the investigator. Performing an emergency waiver of informed consent study is a major time and financial undertaking. Both sets of regulations have allowances for waiver of documentation of informed consent for minimal risk research. **Implication:** If you do not realize your study is subject to FDA regulation, you might propose a waiver of consent (even for a small part of the study) which is not allowable.

C. **Additional Requirements of FDA-regulated research.**

There are specific regulatory requirements for drug and device research, summarized briefly here:

- i. Drugs. If your research involves drugs, you may need to apply for an Investigational New Drug (IND). You will need to if you are giving any drugs which and are not legally marketed (have not been FDA-approved). If you are giving FDA-approved drugs to subjects as a research procedure, you will need to apply for an IND if the drug is given to a population, in a dose, or via an administration route, that is not strictly describe in the package insert labeling for the drug, and the difference in population/dose/route increases potential risk, or decreases the acceptability of known risks, to subjects. You should think about this issue carefully and frame your arguments to the IRB of why you think it does/does not meet this criterion.
- ii. Devices. If your research collects safety or effectiveness data about a medical device, you may need to apply to the FDA for an Investigational Device Exemption (IDE). IDE applications are reserved for potentially significantly risky devices that pose a significant risk to the health or welfare of the subjects. Most implantable devices will be considered significant risk devices. One way to identify a significant risk device is to ask yourself, “If this device does not function correctly or experiences a complication *in this study*, is there a potential for serious risk to the subject?” Note that “in this study” is an important consideration. A non-invasive device, such as a pulse oximeter, could be considered a significant risk device within the context of a study if it is being relied upon as the only mechanism for diagnosing a

serious condition that it has not previously been shown to be able to detect. As always, device studies are tricky and it is a good idea to talk with COMIRB early on about your study.

If you need to obtain an IND or IDE, obtaining one is not actually as bad as it seems...but approaching the process for the inexperienced investigator is incredibly daunting. If you are in this situation, contact the Clinical Research Support Center, where there is a navigator that can help with this process.

III. HIPAA

The HIPAA rule is a complex law that aims to protect the private health information of patients by restricting what can be done with their information. Routine uses within medical treatment, payment, and operations (TPO) are not restricted, but research use is not considered part of TPO. A full discussion of HIPAA is beyond the scope of this workshop, but here is an attempt to boil it down to what you need to consider in your research.

A. *HIPAA only applies to “covered entities”*

The HIPAA rule does not apply if you are not within a covered entity (or perhaps one of the organizations you are collaborating with on your study is not a covered entity). A “covered entity” basically boils down to a member of the medical provision industry that processes claims/transactions electronically. Hospitals, pharmacies, billing companies, etc. are covered entities. At UCD, almost everywhere is a covered entity with two notable exceptions: the School of Public Health (exempt from HIPAA) and almost the entire downtown UCD campus (not a covered entity).

B. *HIPAA restricts access to, use of, and disclosure of identifiable health information*

HIPAA only covers health-related information that is in identifiable form. “Identifiable” under HIPAA is very inclusive and would include health information labeled with a patient’s initials, date of birth, medical record number, subject’s age (if >89 years old), zip code, or even county. A name alone is not identifiable health information, because there is no information about that person’s health. For research purposes, HIPAA applies if you look at identifiable health information (from hospital records) or try to send any identifiable information outside the institution. It is also important to note that UCD and University Hospital are distinct covered entities under HIPAA; therefore, transferring identifiable data from the medical record (EPIC) to your office computer at UCD is restricted by HIPAA.

C. *Think of HIPAA as a “lock box” specific to each institution*

HIPAA locks identifiable health information from improper use and disclosure within each covered entity, not within a research project. Let’s say your project has two sites, both covered entities. When identifiable health information is released from the first covered entity to the second, the transfer is subject to HIPAA. If that same identifiable information is then released back to the first covered entity, that transfer is also subject to HIPAA. Any transfer between covered entities (either direction) must be authorized in writing by subjects, unless it is waived...

D. *HIPAA can be waived*

Just like informed consent, HIPAA can be waived. Some of the same types of criteria apply in waiving HIPAA; criteria include that the data access or transfer must pose minimal risk to the subjects’ privacy, and it must be impracticable to perform the research without the waiver. If you are interacting with subjects and

obtaining signed informed consent, it would be very difficult to justify waiving HIPAA. Like consent, your arguments for waiving HIPAA must be thoughtful, meaningful in terms of patient protection, and not regarding convenience or difficulty for the investigators. Unlike informed consent, there is no such thing as waiver of documentation of HIPAA...it must either be waived entirely or not.

E. *HIPAA is completely separate from the Human Subject Research Regulations.*

Do not be fooled by the fact that the IRB is the one to review HIPAA compliance of research projects; HIPAA is not part of the Common Rule – it is completely separate. The IRB is usually tasked with reviewing HIPAA out of convenience to the institution (they are already reviewing the research anyway...). Implication: Even a project that does not meet the definition of human subject research or is Exempt human subject research must comply with HIPAA. Also, “identifiable” data under HIPAA may not be considered “identifiable” under the Common Rule when it comes to defining whether you have human subject research. You need to think about your project separately from both a Human Subject perspective and a HIPAA perspective.

IV. Selecting a level of IRB review

There are different levels of review through the IRB; you want to select the appropriate review level to maximize your efficiency in completing the review process. You should select the lowest level of review possible for your research without trying to force it to a lower level than is justifiable. In general, as you read through these different levels of review, the paperwork and review timelines increase.

A. *Exempt.*

Exempt human subject research is actually exempted from regulation, including IRB review. However, each institution can require IRB review to ensure the project truly meets exempt requirements; UCD does require Exempt research to be reviewed by COMIRB. Exempt research is ultra-low-risk research by virtue of what is being studied (completely non-stigmatizing and non-sensitive information) or how data are being recorded (in such a way that data cannot be linked back to the original subjects). There are several categories of research eligible for exemption. Eligible categories can be viewed in detail (and it is important to review the details of any particular category) in 45 CFR 46.101(b), but below is a quick-glance summary:

- 1) Educational research using “normal” educational practices
- 2) Surveys/interviews/observation of public behavior [data recorded are not simultaneously sensitive and identifiable; restriction on child subjects]
- 3) Same as Cat#2, without restrictions if subjects are public officials or seeking public office
- 4) Use of data/records/specimens already in existence at time of submission; data recorded with no links to subject identity
- 5) Research on public benefit programs, specifically commissioned by federal agency
- 6) Taste/Food Quality, consumer acceptance

Exempt research requires the least amount of paperwork (only an abbreviated application form; no protocol is required) and is reviewed by a single Chair that is in the office frequently (shorter turn-around times).

B. *Expedited.*

A project can qualify for Expedited review if it i) poses no more than minimal risk to subjects (see D, below) and ii) its procedures fit entirely into pre-defined eligible categories. Eligible categories can be viewed in

detail (and it is important to review the details of any particular category) at <http://www.hhs.gov/ohrp/policy/expedited98.html>, but below is a quick-glance summary:

- 1) Drugs/devices not needing IND or IDE
- 2) Blood draws, limited volume/frequency
- 3) Biologic specimens collected non-invasively (saliva, nail clippings, voided urine)
- 4) Non-invasive data collection (EKG, EEG, MRI, moderate exercise) – excludes X-ray
- 5) Use of records collected for non-research purposes (check vs. Exempt cat #4)
- 6) Recordings (voice, photo, digital image)
- 7) Survey, interview, test, behavior assessments (check vs. Exempt cat #2)

Expedited research requires more paperwork (full application form and a protocol, just like full board), but is reviewed by a single Chair that is in the office frequently (shorter turn-around times).

C. Full Board.

Anything that does not qualify for Exempt or Expedited review must undergo review by a full, convened IRB panel. The paperwork is no different than Expedited, but committees do not convene as often as individual Chairs are available for review, and so the timelines tend to be longer. A full Application form and protocol are required.

D. Risk Determination.

One of the critical determinants of review level is the risk of the protocol (and in Child research, the greatest risk arm of the study). Anything that is minimal risk has the chance of being eligible for Expedited or Exempt review, whereas anything greater than minimal risk must be reviewed at Full Board. The definition of minimal risk is risk encountered in every-day life of a healthy person. So, filling out questionnaires is and exercising moderately are things that a healthy person may encounter in every-day life; so are blood draws (e.g., going to the doctor for a routine check-up and having routine labs performed). The subjects do not have to be healthy to have a study be determined minimal risk; however, it is important to think of the risk of your procedures in context of your proposed subjects. A blood draw of 30mL may be minimal risk for a healthy subject but not for a trauma patient, whereas a blood draw of 2mL might be minimal risk for both.

V. Other Tips for the COMIRB Application

The COMIRB Application is long, but it has a lot of check-box style answers. It seems arbitrary unless you view it through the lens of section I above. The Application is merely collecting detailed information to address the criteria for approval described in 45 CFR 46.111. Here are some additional tips and considerations:

A. Do not blow off questions.

There is a tendency for investigators to leave questions blank or give superficial text answers to various questions because the answer seems obvious if one has read the rest of the Application, or because the investigator does not understand why the question is being asked. The questions pretty much all have some sort of relevance to the regulations; think about which of the IRB approval criteria a question might pertain (criteria 1-8 in section I above). Give an answer that simultaneously illustrates your understanding of the approval criterion and provides the IRB with information to satisfy that criterion.

B. There is some redundancy in the Application.

An example of redundancy is that you might be asked if your study is “minimal risk” in different places. Section J of the Application deals with risk; there are risk considerations as well in Attachment J (pregnant women) and Attachment H (children) as well, for example. Try not to be annoyed by apparent redundancy. The IRB needs to look at the Application as a whole and in terms of different specific populations. In fact, the answers regarding minimal risk overall and minimal risk to specific populations often differ slightly (but sometimes they do not). Try to remember what the purpose of the section you are completing is, and answer with the type of information the IRB should want to know for that section. For example, the study is minimal risk overall because (Section J)...the study is minimal risk specifically to children because (Attachment H)...

C. *There are certain sections that do not relate to IRB approval criteria.*

Yes, it's true. Not everything requested in the COMIRB Application relates directly to the approval criteria. Some examples include section F (Performance sites, which helps determine what local regulations will apply), some of the questions under section G#2 (which flag the need for additional committee reviews), section N (HIPAA Compliance, which is a separate law), and section S (Clinical Trials compliance, which helps ensure you and the institution stay in compliance with other federal and societal mandates). The reason there are some “extra” items in the COMIRB Application is that the IRB is already reviewing the research; it is more efficient for the institution (and you as well) to have some extra items that are important to institutional compliance in this one location rather than having to establish separate committees (and having you submit to each of the separate committees) for review of these items. COMIRB therefore acts as a gatekeeper for other important review requirements on campus.

D. *Don't guess at answers. Use COMIRB's resources.*

If you are unsure of what a question is asking, don't just insert a guess and hope for the best. Instead, flag all of the questions you are unsure of and take advantage of COMIRB's resources such as Office Hours. COMIRB holds office hours three times per month at various locations around campus (check COMIRB's website for times/locations). Office Hours are an opportunity to meet one-on-one with a regulatory advisor and ask any kinds of question you want. A great use of that resource, then, is to ask “What is the committee trying to understand with this question?” for each of the Application questions you are unsure of. You can also show your proposed answer and ask if it is on the right track. If you get a feedback letter from COMIRB that has unclear or surprising requests, you can also bring it to Office Hours and ask an advisor to help interpret what the committee is struggling with.