Research Compliance Professional's Handbook, Third Edition
1 Research Compliance 101

By F. Lisa Murtha, JD, CHC, CHRC, and Debbie Troklus, CCEP-F, CHC-F, CCEP-I, CHPC, CHRC

As updated by: Nicole Visyak, MS, MA, CCRC and Draco Forte, MEd, CHRC[1]

Introduction

Clinical research compliance has become a major focus area of compliance professionals in recent years. Clinical research is highly regulated and as such, the role of a compliance professional is vital to maintaining compliance with NIH, FDA, ORI CMS and OMB requirements. The laws and regulations related to human subject protections, grant and trial accounting, effort reporting, scientific misconduct, privacy and security and clinical trial billing are highly complex and always evolving. This chapter will outline some of the key compliance issues important in research today.

Informed Consent and Human Subject Protections

Informed consent is one of the most coveted rights in healthcare today. Informed consent for treatment by a provider of healthcare services is well known and understood by most people. Informed consent in a research context has been a topic of much debate and reasonable academic minds have differed with regard to how informed consent for research should be administered to a prospective research subject. Informed consent for research is defined in the Belmont Report[2] and is required to be: informed, understood and voluntary. The federal rules for informed consent are outlined in 45 C.F.R. § 46.116 and 21 C.F.R. Part 50. The rules state that informed consent must contain the following elements:

- Introduction with "this is research"—it must be clear to the subject that they are embarking on a research study and that it is not considered to be "therapy"
- Purpose of the study—what is being studied in the research?
- Description of study procedures—this is "experimental"
- Duration of subject involvement—the length of the study
- Potential risks or discomforts of participation
- Potential benefits of participation—although many institutions include a statement that makes it clear that the individual will be treated appropriately regardless of whether they participate in the research study
- Alternatives—other courses of treatment and/or other research studies that might be appropriate to the disease condition of the participant (if any)
- Confidentiality of records—this statement may include HIPAA language after the HIPAA Privacy Rule Compliance Date (April 14, 2003)

- Compensation for injury statement (for greater than minimal risk studies)
- Contact persons—individuals involved with the study including the name of the Principal Investigator and key study staff
- Statement of voluntary participation—it must be clear that the subject has the right NOT to participate
- One of two statements for research that involves the collection of identifiable private information or identifiable biospecimens (Revised Common Rule provision):
    - Identifiers might be removed from information or biospecimens for distribution or use in future research with additional informed consent
    - Information or biospecimens will not be distributed or used for future research
    - A statement that biospecimens may be used for commercial profit and whether or not subjects will share in the profit (Revised Common Rule provision)
- Unforeseen risks
- Reasons for involuntary termination of participation
- Expected or additional costs to participate or withdraw and information regarding whether there are likely clinical outcomes if the protocol is interrupted
- New findings statement
- A statement regarding whether clinically relevant research results, including individual results will be disclosed to subjects (Revised Common Rule provision)
- Statement that the project may include whole genome sequencing (Revised Common Rule provision)
- Number of subjects projected for accrual
- Payments (incentives)—some individuals believe that it is appropriate to include information related to how much money the Site/Investigator is receiving from the sponsor for each study subject and even a breakdown of costs for each component of care.

The seminal rule of the informed consent document is that it must include all relevant information about the study in language that is understandable to the "reasonable" study subject. Some investigators/sites interpret this rule to mean that the form should be written in language that is understandable to a child with no more than an eighth grade education. It is often the case that research subjects speak languages other than English as their primary language and as such, the forms should be translated into those commonly spoken languages in that geographic region with additional help interpreting them if necessary. While the informed consent document is a useful tool in delivering informed consent to potential subjects, it is merely a tool. Informed consent is, however, not a tool but a PROCESS. The process includes a variety of tools including subject recruitment materials (including advertising/marketing materials), verbal instructions delivered to the subject and his/her familysubject, written materials, and question/answer sessions. It must also include agreement and volunteerism of the subject as documented by signature.

The form that is signed by the potential subject serves as documentation that the informed consent was "informed" as defined by the Belmont Report, but how does one measure "comprehension" and

"volunteerism"? Many of us were brought up to consider our physicians to be between an "angel" and "God." As such, we will do whatever our doctors recommend and many patients will do so to please their physicians. Moreover, when we are sick, we feel vulnerable and will latch onto any treatment pathway that may have a chance to make us feel better, or possibly cure us. In cases of serious illness and possible imminent death, it is hard to imagine what would go through your head, much less, what you really understand when your doctor explains a protocol to you. As such, it is incumbent on the investigator and the study site to use diligence in assuring that their subjects truly understand what they are getting into. One way to accomplish this goal is to incorporate a "monitor" into the informed consent process. Another method is to have the consent process "audited" periodically.

In some respects, informed consent really begins with the recruitment methods utilized by the investigator. Some of the common recruitment methods include: formal referrals and informal word of mouth, health workshops, screenings, health fairs, the internet, direct advertising, community meeting places, computerized databases (although HIPAA may change this in the future), and chart/record reviews. Direct advertising is a common mode of recruitment, which includes flyers, posters, newspaper ads, press releases, television spots, as well as radio ads and websites. Direct advertising must be reviewed by the Institutional Review Board for form, content, and mode of communication; it must not state or imply favorable outcomes; it must not be coercive or use undue pressure and must not be misleading to subjects. Finally, it must not use claims of safety, efficacy, equivalence, or superiority. Remember that patients and their families are savvy and they search on the internet and seek out clinical trial sites as well.

A recruitment payment to subjects is a hotly contested topic these days. The Institutional Review Board must approve all payment strategies. The amount of the payment must NOT be an undue inducement of a person to participate. It is very common for potential subjects to be told that their reasonable costs of participation will be reimbursed. These costs typically include parking, lunch, transportation costs, etc. To the extent that reimbursement is offered to subjects, it is recommended that the reimbursement be made when the expenses are incurred, as opposed to lump sum payments that could be construed as "suspicious," or as a way to offer payment of a co-payment. Government investigators carefully scrutinize these payments, and as such, recruitment payments should be carefully considered and specific to the cost being covered.

Many study sites have incorporated research compliance programs into their repertoire of compliance activities. These programs include a regimen of training, periodic reporting, anonymous ways of reporting issues, discipline, prompt follow up, and auditing and monitoring. In the past, the areas that were typically monitored in research were issues related to funding and grants management of federal grants, and time and effort reporting. Given some of the federal investigations and lawsuits in prestigious institutions around the country, auditing and monitoring of human subject protections is a necessary part of the compliance process. In fact, representatives of the Federal Office for Human Research Protections (OHRP) have publicly stated that investigators and study sites should be proactive in monitoring the area of human subject protections on an ongoing basis.

Implementing an informed consent monitoring process is an easy and low-cost way to evaluate how the investigators and study coordinators are doing. The "monitor" could be the compliance officer, an internal auditor, a peer investigator or peer study coordinator, or frankly almost any individual who is independent of the research study. That individual would begin by reviewing the form used to deliver the informed consent to ensure that it contains all the necessary elements as required by the federal rules. Presumably, this will already have been done in detail by the Institutional Review Board as part of the review of the protocol, but it does not hurt to verify the elements of a consent process. In the spirit of full disclosure, the potential subject should be queried as to whether he/she will allow a "monitor" to sit in on the informed consent discussion. Confidential information as well as "protected health information" as defined by HIPAA will be discussed, and you will want to make sure

that the subject is comfortable with having a "third party" involved in those discussions. The subject's agreement should be documented in the participant's medical record stating that the subject understands and agrees to the consent elements such as protocol treatment and financial costs.

The monitor could begin by assessing the nature of the recruitment of the potential subjects. The "monitor" would document the time and circumstances of obtaining the informed consent (i.e., it is being obtained while the patient is being admitted to the Emergency Department with a life-threatening illness or otherwise potentially under "duress"). To the extent that the potential subject speaks a language other than English, the monitor would ensure that the informed consent document used is translated into the language of the subjects and/or a translator is available. To the extent that the subject or his/her family members ask questions, the monitor would document not only the questions but the answers as well. As a final step, the monitor may ask the subject certain follow-up questions designed to test the subject's understanding of the material delivered to them.

While monitoring the informed consent process is not foolproof in making sure that the subjects truly understand what will happen if they participate in the research and what will happen if they do not participate in the research, it certainly would demonstrate and document the diligence taken by the investigator/study site. The costs for implementing this process either could be borne by the study site, or could be built into the study costs/budget. As for the number of studies to be reviewed and the number of subjects to be monitored, that would be a factor of what resources are available to the study site/investigator. There is no right or wrong answer—any monitoring is better than no monitoring.

FDA and the IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects

OHRP regulations at 45 C.F.R. § 46.116 allow an IRB to waive informed consent requirements if research:

- involves no more than minimal risk to subjects,
- the waiver or alteration will not adversely affect the rights and welfare of the subjects,
- the research could not practicably be carried out without the waiver, and
- when appropriate, the subjects will be provided additional information after participation.

However, FDA regulations only allowed exemptions from informed consent requirements only in life-threatening situations or when requirements for emergency research were met (FDA regulations at 21 C.F.R. §§ 50.23-50.24). Upon passage of the 21st Century Cures Act, the FDA was granted the authority to permit exceptions from informed consent requirements. In July 2017 the FDA released its final guidance for the informed consent exceptions for minimal risk clinical investigations. The FDA has yet to promulgate its own regulations for waiver or alteration of informed consent; but through the guidance document, FDA will not object to an IRB adopting the OHRP requirements for waiver or alteration of consent for FDA regulated research.

Revisions to the Common Rule

The ethical principles (i.e., respect of persons, beneficence and justice) that form the foundation of human subjects protections in the US were codified in OHRP regulations in 1991 with The Federal Policy for the Protection of Human Subjects, also known as the Common Rule. Although enforcement agencies have published supplemental guidance to clarify the rules, advancements in technology, electronic health data, and biological specimen collection/storage, among other changes, have grown beyond the regulations. In January 2017, OHRP revised the Common Rule (45 C.F.R. Part 46, subpart A) so that it better comports with how human subjects

research is conducted in today's world and how it will be conducted in the future.

Key provisions of the revised regulations include: revised informed consent requirements, introduction of broad consent, limited IRB review, reliance on external IRBs, the elimination of waiver of informed consent for recruiting, and the elimination of the requirement for IRBs to review grant applications.

The Common Rule revisions include new additional consent elements that must be included as applicable:

- a statement regarding whether identifiers may be removed from private information or biospecimens and used in future research,
- a statement that biospecimens may be used for commercial profit and whether or not subjects will share in the profit,
- a statement regarding whether clinically relevant research results, including individual results, will be disclosed to subjects, and
- a statement that the project may include whole genome sequencing.

The revised common rule allows for the use of broad consent in lieu of informed consent (for unspecified future research) for storage, maintenance and secondary research use of identifiable private information and identifiable biospecimens. Broad consent must provide a general description of the types of research that may be conducted, it must describe the identifiable private information or biospecimens that might be used, it must provide the period of time that information or specimens may be stored, maintained, and used (which could be indefinite), it must include details as to whether subjects will be informed of the research that may use the subject information or biospecimens, it must describe whether subjects will be informed of the results of the future research, and it must provide a contact person for questions about subjects' information, biospecimens and subjects rights.

Under the revised Common Rule there are now eight (8) exempt categories in45 C.F.R. § 46.104(d)(1-8). Only category 6 remains unchanged from the pre-2018 Common Rule. All others have been either revised, replaced or are brand new. The exempt categories are:

Exempt Category	Changes
Category 1: Research conducted in established or commonly accepted educational settings that involve normal educational practices	This has been revised to include a statement to clarify educational practices "that are not likely to adversely impact students' opportunity to learn"
Category 2: Research that only includes interactions involving educational tests, surveys, interviews or observations of public behavior	This has been revised so that research is exempt if one of three criteria is met (not identifiable, does not pose a risk if disclosed, no risk if there is limited IRB review); also, the revised category now includes visual or auditory recording

Exempt Category	Changes
Category 3: Research involving benign behavioral interventions in conjunction with the collection of information from adult subjects	This is a new category that defines benign behavioral interventions 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"
Category 4: Secondary research for which consent is not required	This has been revised to clarify that the use of identifiable private information or biospecimens does not require informed consent if: a) the identifiable information or biospecimens are publicly available, b) if the information is recorded by the investigator in such a way that subject identity cannot readily be ascertained, c) research use of identifiable health information is in accordance with HIPAA, d) research is conducted by or on behalf of a federal department or agency
Category 5: Research and demonstration projects conducted or supported by a federal department or agency	This has been revised to allow research supported by a federal agency to qualify for this exemption
Category 6: taste and food quality evaluation and consumer acceptance studies	This criterion is unchanged
Category 7: Storage or maintenance for secondary research for which broad consent is required	This is a new category
Category 8: Secondary research for which broad consent is required	This is a new category

Other revisions include the limited IRB review provision that removes the requirement for continuing review for studies that received expedited initial review and for intervention studies that have completed intervention and are only analyzing data or observational follow-up. The new rule introduces the requirement for the use of a single IRB for cooperative research in the US. Note that this does not apply when more than a single IRB is required by law (tribal law) or when federal sponsor documents that use of a single IRB is not appropriate. The revised Common Rule eliminates the requirement for the IRB to grant a waiver of informed consent to obtain information or biospecimens for screening, recruiting or determining eligibility. Another revision of note is the elimination of the requirement that IRBs review federal grant applications or funding proposals related to the research.

The Department of Health and Human Services delayed the effective and compliance date of the Revised Common Rule until January 21, 2019. However, the single IRB provisions compliance date is January 20, 2020.